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Ward et al.

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(54) **IMPLANTABLE DEVICE FOR MONITORING CHANGES IN ANALYTE CONCENTRATION**

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(22) Filed: **Nov. 28, 2000**

Related U.S. Application Data

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(51) **Int. Cl.**[7] **A61B 5/05**

(52) **U.S. Cl.** **600/345**; 600/347; 204/415

(58) **Field of Search** 600/345–350, 600/353, 355, 357, 364, 365, 363, 377; 204/415

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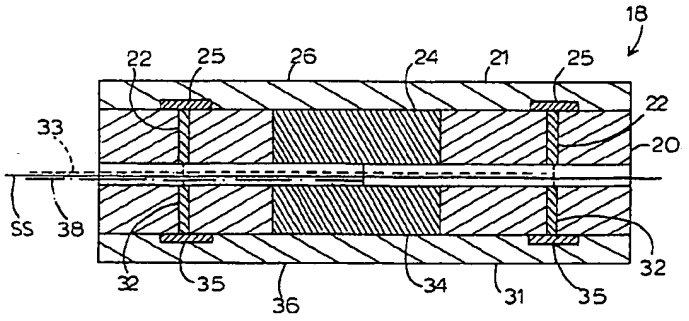
(74) *Attorney, Agent, or Firm*—Stoel Rives LLP

(57) **ABSTRACT**

The invention provides an electrochemical sensor system for measuring analyte concentrations in a fluid sample. The invention is particularly useful for measuring analytes such as glucose in a patient. An implantable glucose sensor includes a disc-shaped sensor body containing multiple anodes on opposing sides of the sensor body. Electrodes including an anode and a cathode are connected to a transmitter which transmits radio signals to an external receiver and computer where data is processed to yield glucose concentration figures. An enzyme layer coating the anodes specifically reacts with glucose to increase signals generated by the anodes in response to the presence of glucose. In an alternate embodiment, some of the anodes are coated with the enzyme to generate a first signal, and other anodes that are not coated generate a second signal for comparison with the first signal to eliminate effects of interfering substances on the accuracy of the glucose measurement.

13 Claims, 8 Drawing Sheets



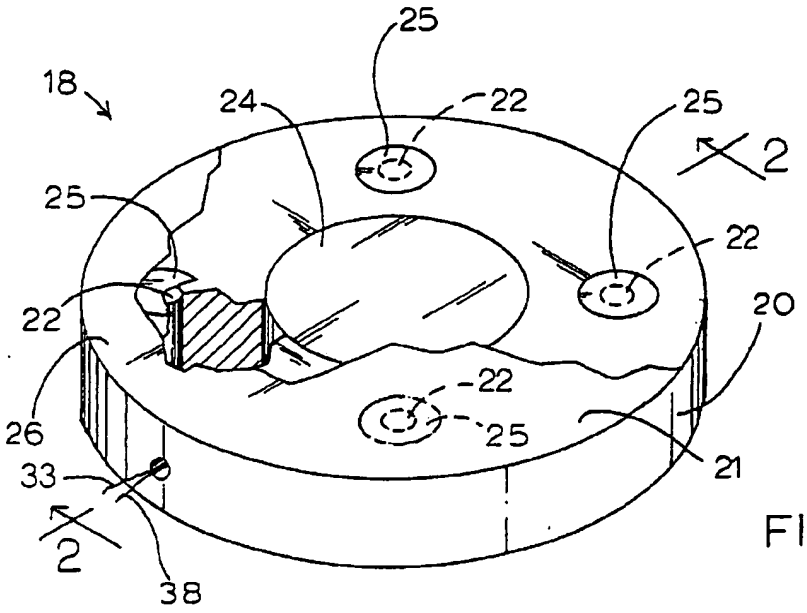


FIG.1

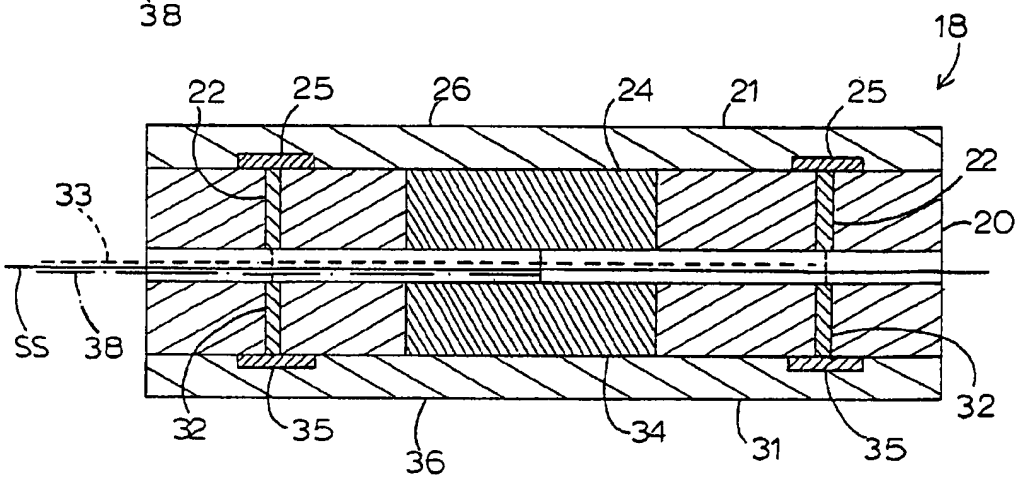


FIG. 2

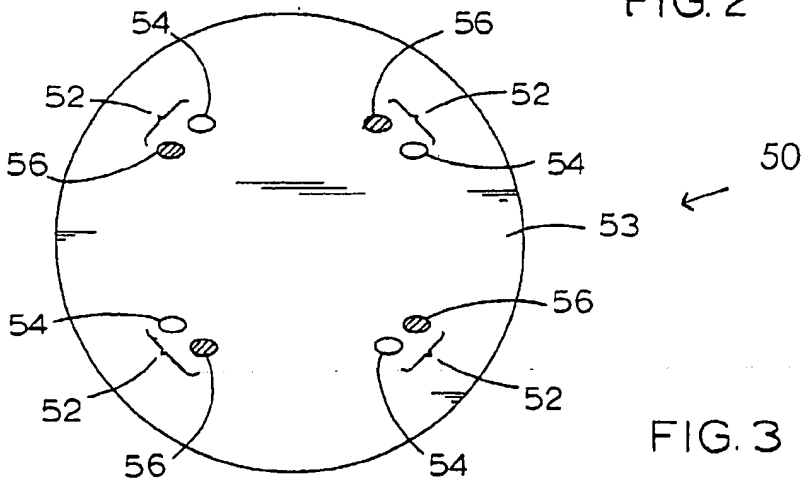


FIG. 3

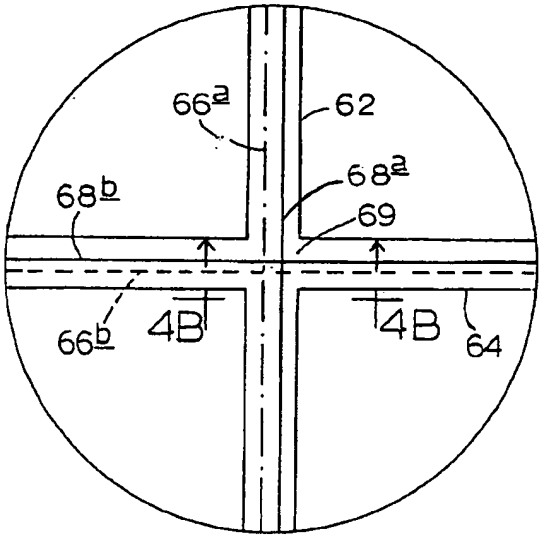


FIG.4A

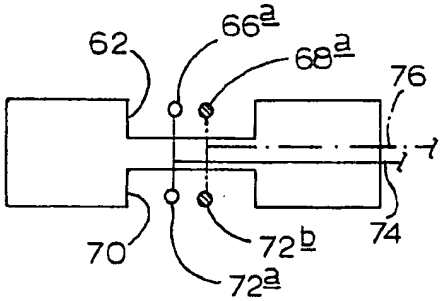


FIG.4B

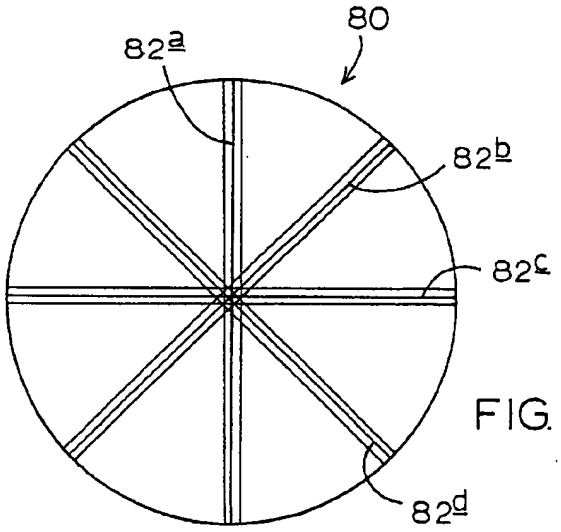


FIG.5

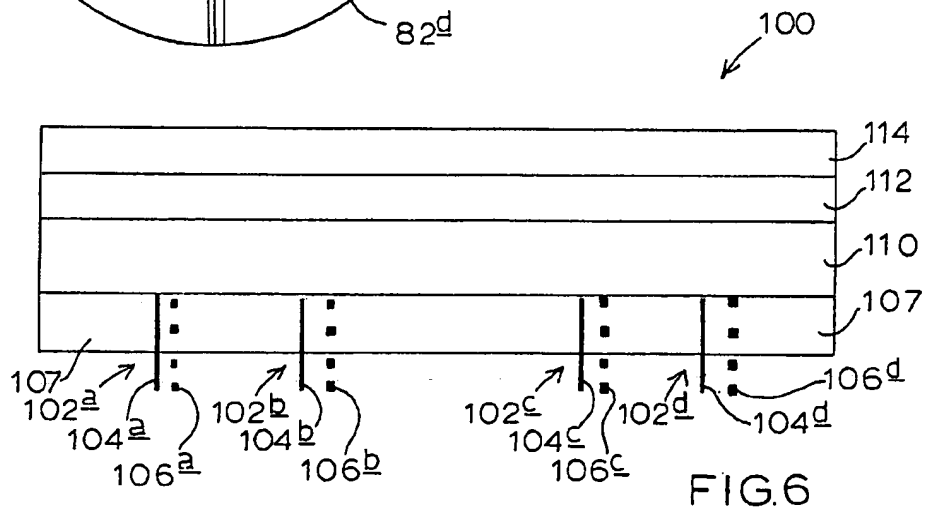


FIG.6

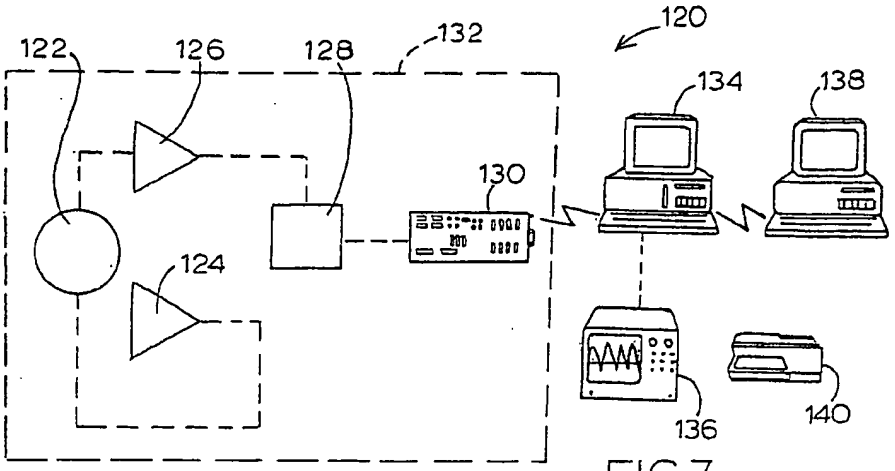


FIG.7

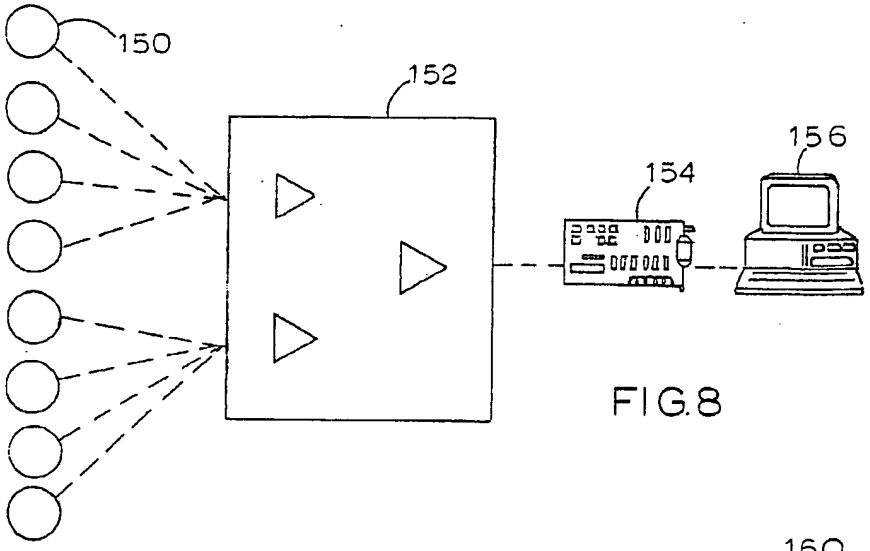


FIG.8

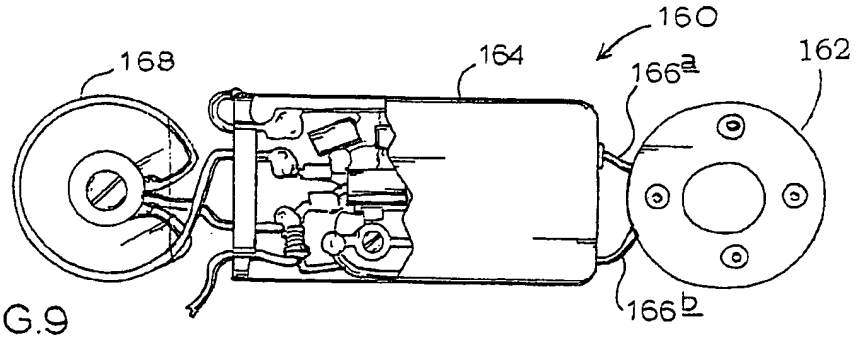


FIG.9

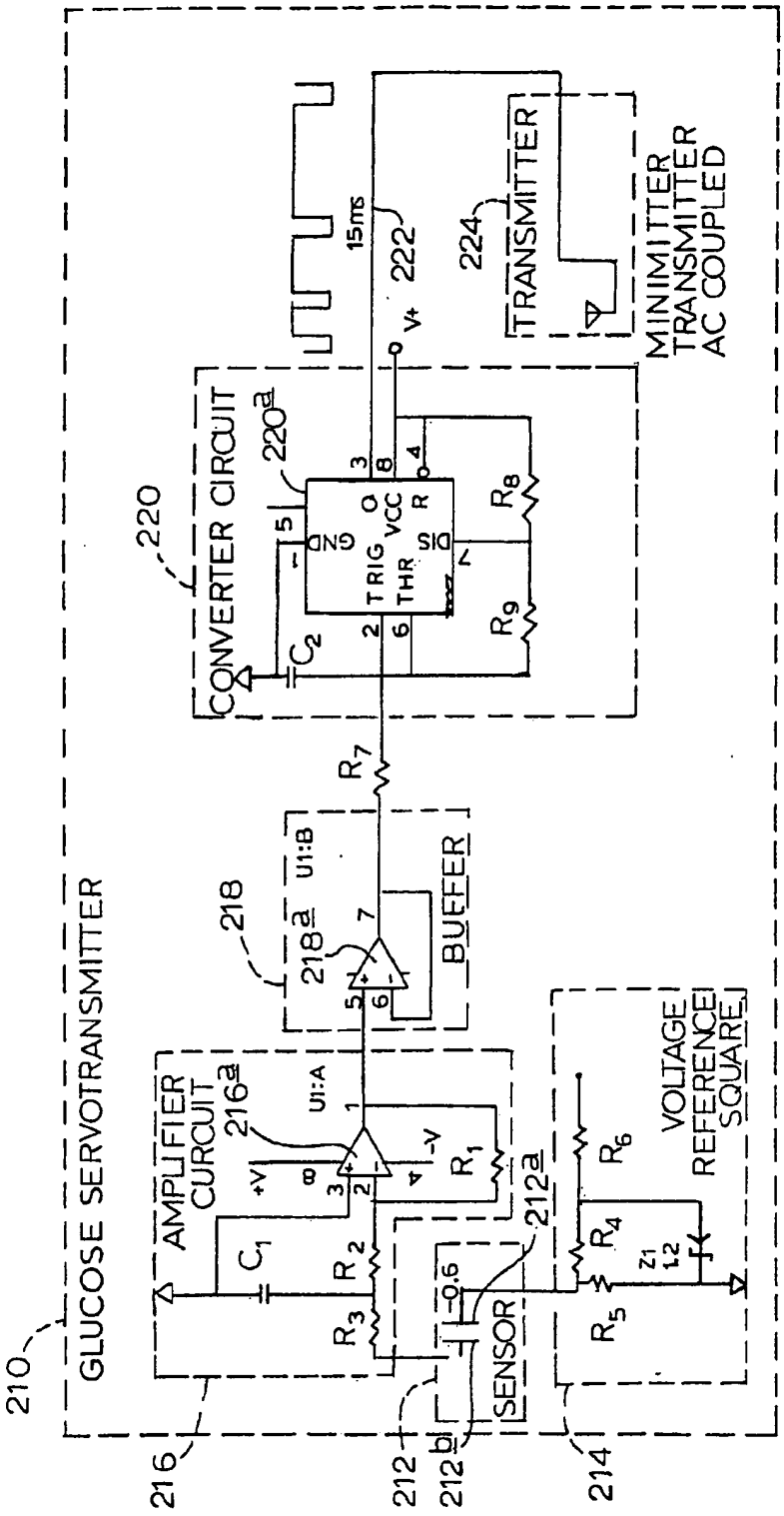

GLUCOSE SERVOTRANSMITTER
210
AMPLIFIER CIRCUIT
216a
U1:A
+V
-V
C1
R1
R2
R3
216
CONVERTER CIRCUIT
220
220a
TRIG
THR
GND
VCC
SIG
R
Q
C2
R8
R9
15ms
222
V+
TRANSMITTER
224
MINIMITTER TRANSMITTER AC COUPLED
R7
BUFFER
218
218a
U1:B
212
212a
212b
SENSOR
-0.6
VOLTAGE REFERENCE SQUARE
214
R4
R5
R6
Z1
1.2

FIG. 10

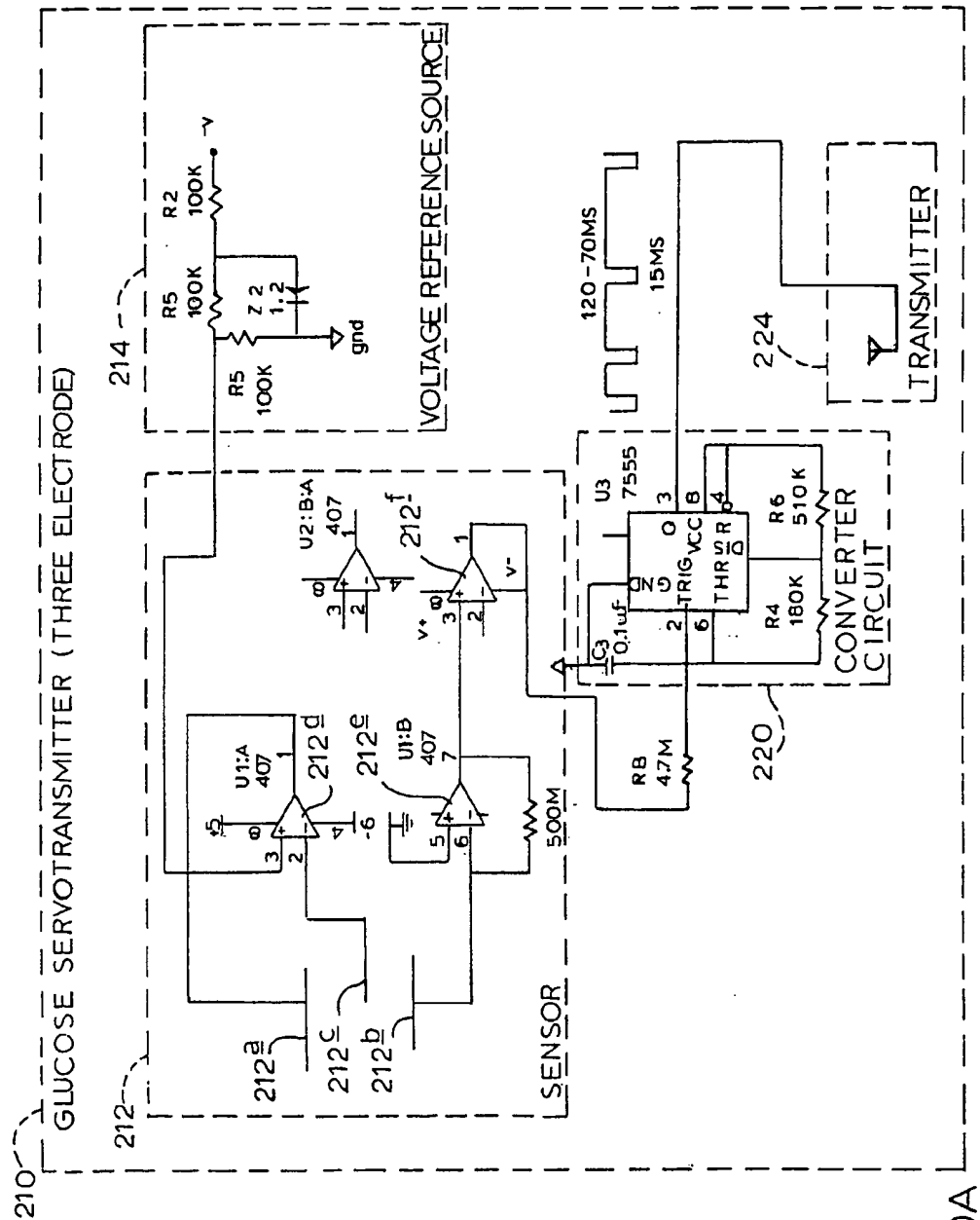

GLUCOSE SERVOTRANSMITTER (THREE ELECTRODE)
210
212
SENSOR
212a
212b
212c
212d
212e
212f
U1:A 407
U1:B 407
U2:B:A 407
500M
214
VOLTAGE REFERENCE SOURCE
R2 100K
R5 100K
R5 100K
Z 2 1.2
gnd
-V
V+
V-
U3 7555
120-70MS
15MS
0.1uf
R8 4.7M
R4 180K
R6 510K
CONVERTER CIRCUIT
220
224
TRANSMITTER

FIG. 10A

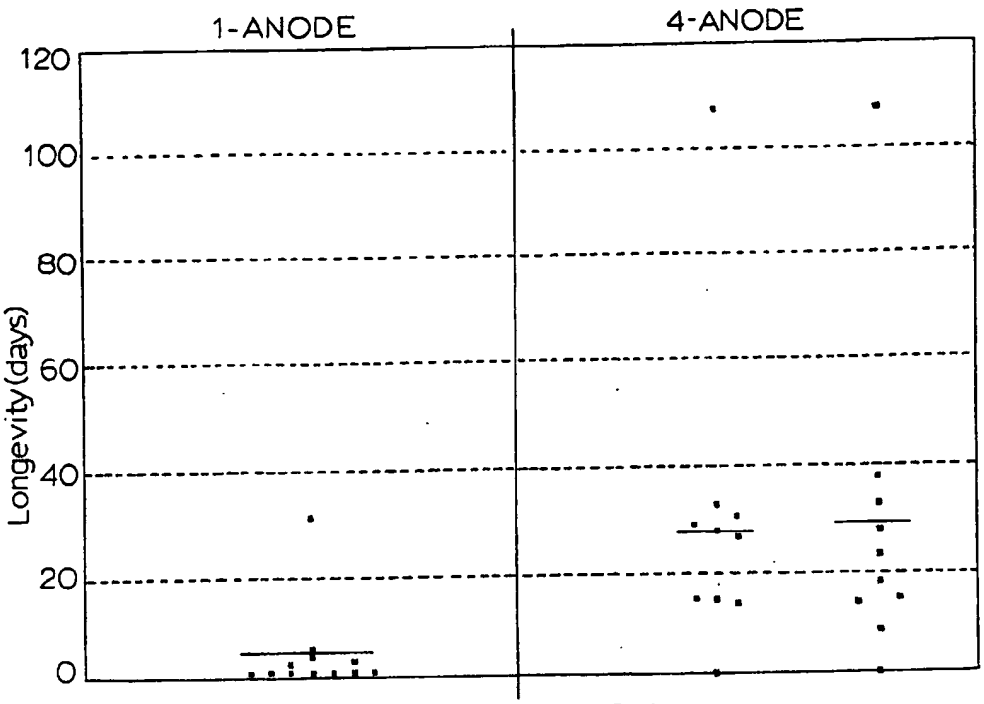

1-ANODE
4-ANODE
120
100
80
60
40
20
0
Longevity (days)

FIG.11

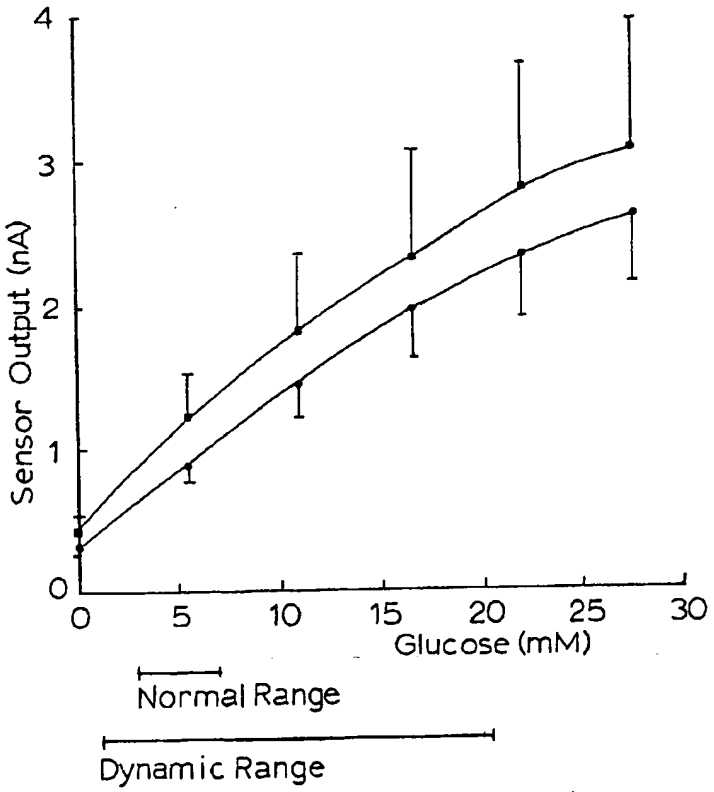

4
3
2
1
0
Sensor Output (nA)
0
5
10
15
20
25
30
Glucose (mM)
Normal Range
Dynamic Range

FIG.12

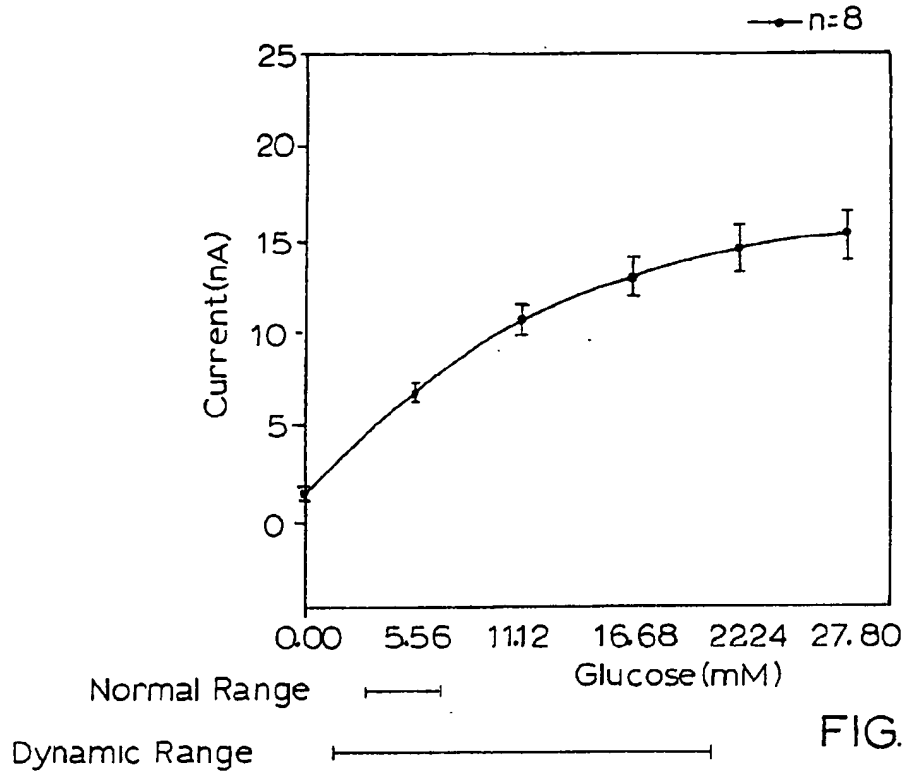

n=8
25
20
15
10
5
0
Current(nA)
0.00
5.56
11.12
16.68
22.24
27.80
Glucose(mM)
Normal Range
Dynamic Range

FIG.13

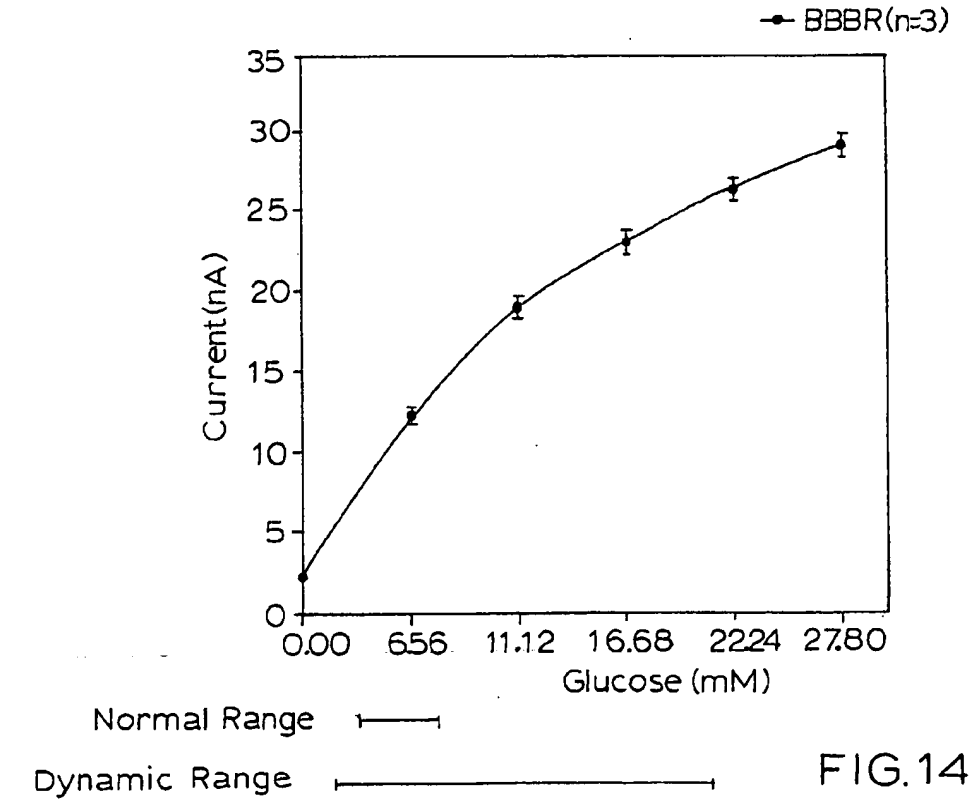

BBBR(n=3)
35
30
25
20
15
10
5
0
Current(nA)
0.00
6.56
11.12
16.68
22.24
27.80
Glucose (mM)
Normal Range
Dynamic Range

FIG.14

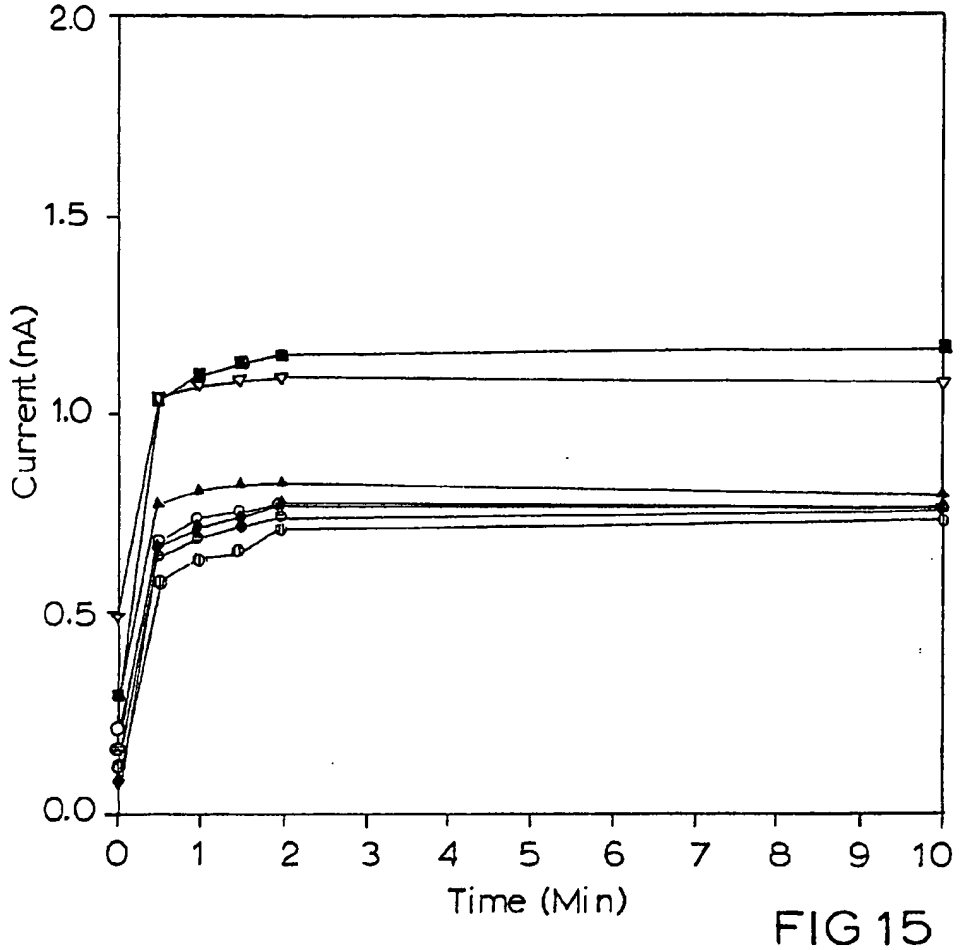


FIG 15

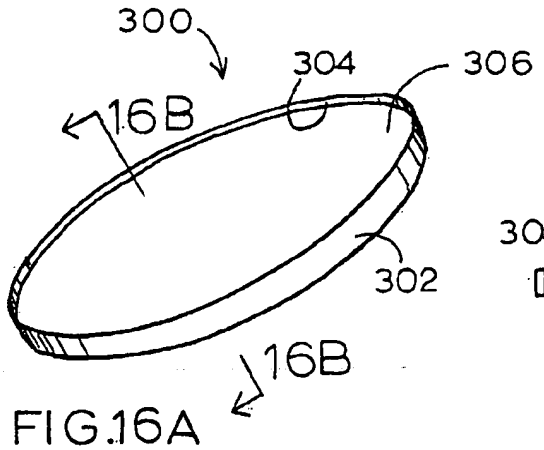


FIG.16A

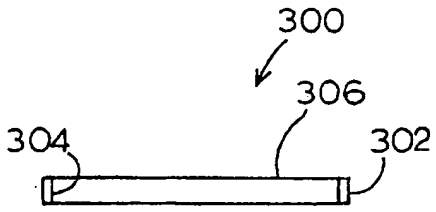


FIG.16 B

IMPLANTABLE DEVICE FOR MONITORING CHANGES IN ANALYTE CONCENTRATION

RELATED APPLICATIONS

This is a divisional application claiming priority from U.S. application Ser. No. 09/083,520, filed May 22, 1998, which is a continuation-in-part national phase of International Application No. PCT/US96/18724, filed Nov. 21, 1996, which is a continuation-in-part of application Ser. No. 08/561,972, filed Nov. 22, 1995, now U.S. Pat. No. 5,711,861.

FIELD OF THE INVENTION

The invention relates to electrochemical systems for measuring analyte concentration. In particular, the invention involves a sensor including electrodes under a semi-permeable membrane for monitoring analyte concentrations in fluids surrounding the sensor.

BACKGROUND OF THE INVENTION

There are many instances when it is necessary to monitor the concentration of molecules ("analytes") in a fluid. For example, glucose levels must be frequently monitored in persons with diabetes so that appropriate doses of insulin can be administered in a timely manner. Many other analytes are measured commonly in human blood and in other fluids.

A variety of methods and devices for measuring analytes in fluids have been devised. One such device, referred to as an electrochemical sensor, typically includes oppositely charged electrodes under a semi-permeable membrane. Depending on what analyte is being monitored, membranes, enzymes and/or other appropriate materials are provided around the electrodes so that analyte reaction and transport from the fluid surrounding the sensor is controlled. Oxidative and reductive reactions take place at or near the electrodes, thus causing electrical potentials measured as changes in current which may be correlated to the concentration of analyte in the fluid.

Electrochemical sensors have been used to measure glucose in human blood. Most of these sensors are designed to measure glucose in a blood sample which has been drawn or extracted from the patient. For patients such as people with diabetes who must test blood glucose levels as often as several times per day, the regular blood drawing process (typically by finger tip puncture) becomes quite cumbersome, messy and even painful. The person with diabetes must carry special equipment for extracting blood. Some patients fail to test as frequently as they should because of problems associated with the blood extracting process.

Therefore, it has been recognized for a long time that an implanted glucose sensor would offer the important advantage of avoiding the need for repeated blood extraction. However, there are other problems which must be addressed with an implantable sensor. First, there must be a mechanism for accessing raw electrical data generated by the sensor under the patient's skin. Protruding wires are undesirable because they are cumbersome, prone to causing infection and sometimes painful. Accordingly, it is preferable to include a wireless data transmission (telemetry) device coupled to the sensor in a single implantable unit so that no trans-dermal wires are required.

Second, an implanted sensing unit may cause internal trauma, i.e., bruising or bleeding from the patient's routine movement or contact with his or her environment, especially if the sensing unit is large or thick or if it is geometrically shaped with any sharp points or edges.

Another problem associated with implantable sensors is that over time (days and weeks) a cellular coat tends to develop around the sensor which may eventually block the analyte of interest from contacting the electrodes, thus causing the sensor to fail.

For these reasons, and perhaps other reasons, researchers in the field have been unsuccessful in their attempts to produce an implantable sensor unit which is capable of functioning satisfactorily for a sufficient period of time to justify the expense and inconvenience of producing and surgically implanting the sensing hardware.

A viable implantable glucose sensor should provide reliable performance for at least 1–2 months, preferably three months or more. During its useful life, the device should generate a predictable dose response over a concentration range of approximately 40 to 400 milligrams per deciliter (mg/dl). The device should exhibit a lag time between a concentration change and the resulting signal output of less than 20 minutes, preferably less than 10 minutes. The sensor should be relatively insensitive to potential interfering substances such as ascorbic acid and acetaminophen. The device should be relatively accurate for at least several days after calibration (stability). Glucose measurement with the sensor should be precise to at least within approximately 10 mg/dl. The sensor should be incorporated in an implantable unit which is capable of wireless data transmission, and which is dimensioned so as to minimize surgical complication and risk of pain, bruising or other internal trauma.

SUMMARY OF THE INVENTION

The objectives stated above are achievable with the device and system of the present invention which includes a device for electrochemically sensing changes in the concentration of an analyte of interest.

In one embodiment of the invention, the device includes a sensor body having two opposing sides. Each side of the body includes at least one, preferably several, anode(s) and at least one cathode spaced apart from each other and covered by a membrane which is semi-permeable to the analyte of interest. In a preferred sensor design for measuring glucose, plural anodes are disposed on two opposing sides of a disc-shaped sensor body. The anodes are covered by an enzyme layer including glucose oxidase and an outer semi-porous membrane layer made of material such a Parylene™ ("PPX") or Chronoflex™ AR ("CAR").

In another embodiment of the invention, the sensor body contains a plurality of electrode pairs, each pair including an anode and a cathode. The electrode may take the form of points or lines. In one design, linear electrodes are arranged in a "spoke-like" configuration. The electrode pairs preferably are disposed on both sides of the body.

An implantable glucose sensor, according to the present invention, may be electrically coupled to a transmitter which includes a power source, for example a battery. The transmitter is capable of converting data signals from the sensor into corresponding radio signals. A receiver is provided remotely from the sensor for receiving the radio signals. A processor is connected to the receiver and used to interpret the radio signals, to yield analyte concentration figures.

The present invention also provides a method of making an analyte sensor. A substantially disc-shaped body is provided with two opposing sides. At least one cathode and plural anodes are created on each side of the body. A semi-permeable membrane is deposited on the electrodes.

When the method is employed to make a glucose sensor, the enzyme layer including glucose oxidase is created between the anodes and the semi-permeable membrane. An interferent retarding layer may be created between the anodes and the enzyme layer.

DESCRIPTION OF THE FIGURES

FIG. **1** is a partially cut-away perspective view of an analyte sensor in accordance with a preferred embodiment of the present invention.

FIG. **2** is a cross-sectional view of the sensor shown in FIG. **1**.

FIG. **3** is a top view of an analyte sensor in accordance with a second embodiment of the present invention.

FIG. **4A** is a top view of an analyte sensor employing linear electrodes in accordance with a third embodiment of the present invention.

FIG. **4B** is a partial cross-sectional view of the sensor shown in FIG. **4A**.

FIG. **5** is a top view of another analyte sensor in accordance with a fourth embodiment of the present invention.

FIG. **6** is a schematic side view of a glucose sensor including an interferent retarding layer.

FIG. **7** is a schematic flow chart of an analyte monitoring system including sensor, electronics, telemetry and computing components.

FIG. **8** is a flow chart of an analyte monitoring system including multiple sensors linked in parallel to the same data acquisition and processing components.

FIG. **9** is a top view of an implantable unit including a glucose sensor and radio telemetry device.

FIGS. **10** and **10A** are circuit diagrams illustrating circuitry employed in glucose sensors of the present invention.

FIG. **11** is a graph demonstrating the results of an experiment conducted to compare longevity of single and multiple anode sensors.

FIG. **12** is a graph illustrating the results of an experiment conducted to compare sensor performance pre-implant versus post-explant.

FIG. **13** is a graph showing the average glucose dose response and repeatability of eight sensors each of which was coated with PPX.

FIG. **14** is a graph showing the average glucose dose response and repeatability (n=3) for a sensor coated with CAR.

FIG. **15** is a graph presenting the results of an experiment conducted to determine the relative response times (T90s) for eight sensors each of which was coated with PPX.

FIG. **16A** is a perspective view of a disc-shaped implantable sensor with a circumferential polymer matrix for carrying and slowly releasing a fibrotic capsule interference inhibitor.

FIG. **16B** is a cross-sectional view of the sensor shown in FIG. **16A**.

DEFINITIONS

An electrode means an electric conductor, which may be an anode or a cathode.

An anode is a positively charged conductor.

A cathode is a negatively charged conductor.

A sensor is a device which detects changes in analyte concentration in a fluid surrounding the sensor. A sensor includes an anode and a cathode, chemically modified and physically arranged to produce electric signal changes which can be interpreted by sensing electronics to measure analyte concentration changes over a specified concentration range.

An analyte is a molecule of interest in a fluid surrounding a sensor.

An electrometer is a device which senses small changes in current and translates amps to volts.

A transmitter or radio telemetry device is a device which transmits radio signals.

A receiver is a device capable of receiving radio signals from a transmitter.

A body or sensory body is a housing for supporting and containing sensor components.

A semi-permeable membrane or analyte selective coating is a material which permits controlled transfer of an analyte through the material.

Interfering substances are molecules in the fluid surrounding the sensor, which are potentially detectable by the sensor possibly causing an inaccurate or erroneous analyte concentration determination.

An interferent retarding layer is a material employed in a sensor to either physically or chemically neutralize a potential interfering substance, thereby preventing the substance from interfering with the desired analyte concentration determination.

Chronoflex™ AR ("CAR") is a trade name for a carbonate based polyurethane available from Cardiotech, Inc., Woburn, Mass.

Parylene™ ("PPX") is a trade name for polyparaxylxylene available from Union Carbide.

DESCRIPTION OF THE INVENTION

We have invented an analyte sensing system including an implantable sensor which exhibits significantly improved performance characteristics over a longer functional life in comparison to prior sensing systems. Our invention has also resulted in improvements which are useful in non-implantable sensors and other sensing applications. The model for illustrating important principles of the present invention, as discussed in detail below, relates to implantable glucose sensors.

Prior implantable glucose sensors do not function satisfactorily over a long enough period to justify the cost and complication of implantation. We have observed that increasing the number of anodes, or electrode pairs, or total number of sensors connected in parallel, and by distributing the anodes on different sensing faces of one or more sensors, greatly enhances the functional life span of an implantable glucose sensing system. Our experiments confirm that redundancy enhances sensor unit function. Other problems with prior electrochemical glucose sensors relate to electrical drift and instability. The redundancy of the present invention, i.e., multiple anodes or multiple sensors distributed on multiple faces of one device, appears to significantly reduce such drift. A possible reason for this is that each individual sensing unit may have its own fundamental instability, and that by incorporating multiple sensing units into a single system, an averaging effect tends to cancel out random drift associated with individual sensors.

FIGS. **1** and **2** illustrate a disc-shaped glucose sensor which has two opposing faces, each of which has an identical electrode configuration. One of the faces can be seen in the partially cut-away perspective view in FIG. **1**. Sensor **18** includes a disc-shaped body **20**. On planar face **21**

of sensor **18**, four platinum anodes **22** are symmetrically arranged around centrally disposed silver chloride cathode **24**. Each anode **22** is covered by an enzyme layer **25** including the active enzyme glucose oxidase and stabilizing compounds such as glutaraldehyde and bovine serum albumin (BSA). A semi-permeable membrane layer **26** covers all of the electrodes and individual enzyme layers. The thickness and porosity of membrane layer **26** is carefully controlled so as to limit diffusion and/or transport of the analyte of interest (glucose) from the surrounding fluid into the anode sensing regions. The mechanism of selective transport of the analyte of interest through the membrane may involve one or more of the following principles: molecular size exclusion, simple mass transfer, surface tension phenomena and/or other chemically mediated processes.

A cross-section of sensor **18** is shown in FIG. **2**. Sensor **18** has a plane of symmetry SS which is normal to the plane of the figure. Under face **31** of sensor **18** anodes **32** are spaced equidistantly apart from cathode **34**. Enzyme layers **35** cover anodes **32**. A semi-permeable membrane **36**, preferably PPX or CAR, covers the enzyme layers and electrodes. Each of anodes **22** and **32** are connected to a common anode wire **33** which leads out of the sensor for electrical connection to an electrometer. Similarly, each of cathodes **24** and **34** are connected to a common cathode lead **38** which leads out of sensor **18** for electrical connection to the electrometer.

FIG. **3** shows an alternative embodiment of the invention in which a plurality of electrode pairs are presented on both sides of a disc-shaped sensor. Only one side of the sensor is shown in FIG. **3**. The enzyme and semi-permeable membrane layers are removed to permit viewing of the electrode configuration. Sensor **50** (an "8-in-1 sensor") includes eight electrode pairs **52**, only four of which are shown distributed around surface **53** of sensor **50**. Each electrode pair **52** includes an anode **54** spaced apart from a cathode **56**. Similar to the first embodiment described, all of anodes **54** are linked to a common anode wire (not shown) which extends outside the body of sensor **50**. All of cathodes **56** are connected to a common cathode wire which extends outside sensor **50**. The anode and cathode wires leading out of sensor **50** are eventually connected to an electrometer.

FIGS. **4A**, **4B** and **5** illustrate a different type of anode and cathode configuration in which each electrode is exposed along a linear path on the sensor surface. In FIG. **4A**, sensor **60** is formed with troughs **62** and **64** that intersect at right angles in the center of the sensor surface. Within trough **62** linear anode **66***a* runs parallel to linear cathode **68***a*. Similarly, in trough **64** linear anode **66***b* runs parallel to linear cathode **68***b*. The electrodes are insulated from each other in the junction area **69** where the troughs intersect. FIG. **4B** shows a cross section through trough **62** in the junction area of the sensor. Trough **62** has a corresponding trough **70** in the opposite side of sensor **60**. In trough **70**, linear anode **72***a* runs parallel to linear cathode **72***b*. Anodes **66***a* and **72***a* are both connected to common anode wire **74**. Linear cathodes **68***a* and **72***b* are connected to common cathode wire **76**. Anode wire **74** and cathode wire **76** lead out of sensor **60** for connection to an electrometer. The troughs are preferably filled with an electrolyte gel.

As shown in FIG. **5**, the concept of employing linear electrodes across opposing faces of the sensor can be extended to provide more electrode sensing area or "spokes". In FIG. **5** sensor **80** is essentially the same as sensor **60** (FIGS. **4A** and **4B**) except that it has two additional troughs, each containing another pair of parallel linear electrodes. Sensor **80** includes trough **82***a*, **82***b*, **82***c* and **82***d*, all of which intersect in the center of sensor **80**. Each of the troughs **82***a–d* contains a pair of linear electrodes (anode and cathode) encased in electrolyte gel. All of the linear anodes in sensor **80** are connected to a common anode wire, and all of the linear cathodes are connected to a common cathode wire. Other anode patterns which function effectively include a circle, concentric circles or a spiral.

FIG. **6** shows schematically a cross section through multiple layers on one side of a sensor. Sensor **100** includes an electrode configuration similar to the embodiment illustrated in FIG. **3**. Electrode pairs **102***a–102d* each include a cathode **104***a–104d* and an anode **106***a–106d*, respectively.

An electrolyte gel **107** surrounds the anode-cathode pairs, thus providing a faster and more sensitive response to changes in glucose concentration. The gel may be produced from methacrylate compounds or from collagen. For example, a methacrylate compound may be dissolved in an organic solvent and then deposited around the anode-cathode pairs. The solvent is then evaporated. Phosphate buffered saline with KCl is then added to the gel to swell the methacrylate compound. In the 8-in-1 embodiment (FIG. **3**), the electrolyte gel is placed over the surface of the electrode pairs and/or the gel is injected into the drilled cylinder in which the electrode pair is situated. Similarly, in the radial spoke-type embodiments shown in FIGS. **4** and **5**, the troughs maybe filled with electrode gel.

Layer **110** is deposited immediately on top of the electrodes for the purpose of minimizing or avoiding interference due to the presence of interfering substances which may be present in the sample fluid. Enzyme layer **112** is deposited on top of interferent retarding layer **110**. Enzyme layer **112** includes, in the case of a glucose sensor, glucose oxidase, and is applied in a solution of glutaraldehyde and bovine serum albumin (BSA), either by placement of a drop over each electrode pair, or by dip-coating the entire sensing unit, or by spin-coating. Semi-permeable membrane **114** is deposited on top of enzyme layer **112** for the purpose of controlling diffusion of glucose from the sample fluid into the electrode region of the sensor. PPX at a thickness of about 3,000–6,000 angstroms works well for this purpose. The preferred thickness of PPX layer **114** is 4,000–5,000A. Other suitable materials for semi-permeable membrane **114** include CAR and polyurethanes such as Tecoflex™, Techothane™, Carbothane™ and Cook™ composite.

A number of interferents which exist in human plasma can be oxidized at the anode when connected to sensor electronic circuitry, thus registering a current which interferes with the signal of interest, i.e., signal generated due to the presence of glucose. Potential interferents include, for example, uric acid, ascorbic acid and the common analgesic drug acetaminophen. Interferents tend to pass freely through semi-permeable membrane **114** and enzyme layer **112**. The compounds can be blocked from reaching the electrodes by interfering retarding layer **110** which has a pore size big enough to allow diffusion of hydrogen peroxide (H_2O_2), a product of glucose oxidation in layer **112**, yet small enough to exclude compounds such as uric acid, ascorbic acid and acetaminophen from reaching the electrodes.

A preferred-material for the interferent retarding layer **110** is PPX. PPX is a hydrophobic compound which is applied to the substrate in a vacuum deposition chamber. The deposition process can be carefully regulated to form an interferent retarding layer of precise thickness (5,000–8,000A) prior to depositing the enzyme layer. CAR also appears to be a suitable material for use as an interferent retarding layer.

Paired sensors can also be used to provide an alternate method of avoiding interfering currents from oxidizable,

non-glucose compounds. For example, a first, coated sensor is a standard sensor coated with glucose oxidase. The first sensor measures glucose and interfering compounds. A second, uncoated sensor is the same as the first sensor except it does not have glucose oxidase and thus detects only the interfering compounds. The magnitude of the current from the uncoated sensor is subtracted from the magnitude of the current from the coated sensor to yield a signal which represents the glucose concentration independent from interfering substance concentrations.

In practice this subtraction method can be implemented in ways other than the paired sensors described above. A second alternative embodiment of a device that employs the subtraction method is based upon the sensor arrangement of FIGS. **1** and **2**. In this embodiment the four platinum anodes **22** on planar face **21** are covered with enzyme layer **25** and connected to a first common anode wire (not shown). Unlike sensor **18** shown in FIGS. **1** and **2**, anodes **32** under face **31** of this second alternative embodiment are not covered by enzyme, and are connected to a second common anode wire (not shown). Cathodes **24** and **34** are connected to common cathode wire **38** as shown in FIG. **2**. The common cathode wire serves as a reference for the first and second common anode wires. The first common anode wire carries a first signal that can be compared with a second signal carried by the second common anode wire to eliminate the effects of interferents and isolate a signal representing the concentration of the analyte of interest.

A third alternative embodiment of a device using the subtraction method is also based upon the sensor arrangement of FIGS. **1** and **2**. In this third embodiment, two of the four anodes **22** on face **21** and two of anodes **32** on face **31** are covered with enzyme layer **25**. The other two anodes on each face are not covered by enzyme. The anodes on faces **21** and **31** that are covered with enzyme are all connected to a first common anode wire. The anodes that are not covered with enzyme are all connected to a second common anode wire.

In a fourth alternative embodiment, the sensor device is based upon the sensor of FIG. **3**. In this fourth embodiment, one half of the total number of electrode pairs **52** have anodes covered by an enzyme layer, with each such anode connected to a first common anode wire (not shown). The other half of the total number of electrode pairs have anodes that are not covered by enzyme, and each of these anodes are connected to a second common anode wire.

Skilled persons will realize that this subtraction method can be implemented in any embodiment of a glucose sensor having multiple anodes. In addition it is believed that the method could be successfully implemented using a quantity of enzyme-coated anodes that is different from the quantity of uncoated anodes, by applying the appropriate signal amplification or data translation techniques. Skilled persons will understand that the sensor can also include a separate wire for each cathode and each anode instead of the common anode and common cathode wires described above. Separate wires facilitate troubleshooting of the sensor by a repair person or technician. When a sensor is implanted with a radio transmitter unit, multiple wires allow the sensor's transmitter to transmit multiple signals to a receiving computer or acquisition computer that can filter the signals to correct for malfunctioning electrode pairs or anodes. The telemetry feature of an implantable sensor is described below in further detail.

The sensor designs described above can also be modified so that the electrodes detect fluctuations in oxygen concentration which is relatable to glucose concentration. In this approach, the sensor monitors oxygen disappearance instead of hydrogen peroxide appearance. First, the polarity is changed so that the platinum electrodes (previously referred to as "anodes") become negatively charged with respect to the silver chloride (previously referred to as the "cathode"), i.e., the platinum becomes the cathode and the silver chloride becomes the anode. Second, a membrane is deposited immediately on top of the cathode and anode which is permeable to oxygen but not to larger molecules. The outer membrane and the enzyme layer remain the same. In this configuration, glucose concentration results in a decrease in oxygen concentration at the negatively charged electrode.

Another embodiment of the invention has a modified outer membrane. It is possible that functional longevity of implantable sensors is limited because the outer membrane tends to become "fouled," i.e., plugged or covered by molecules and/or other cellular materials. Accordingly, one adaptation of the invention employs a changing membrane so that the outer membrane can be renewed over time without disrupting operation of the sensor. In the modified sensor, the outer membrane is a solid sheet which can be moved across the face of the sensor where the electrodes are exposed. For example, the membrane can be transferred from one roller to another roller analogous to the way film is transferred inside a camera. A drive mechanism such as a small motor may be included in the implantable unit for driving the rollers.

FIG. **7** shows schematically how an implantable glucose sensor is connected in a glucose monitoring system **120**. Electrodes in sensor **122** are polarized by polarizing circuit **124**. Polarization of the sensor electrodes may be constant or pulsed. Our experiments have shown improvement in sensor performance stability, i.e., maintaining sensitivity and minimizing drift, when polarization is pulsed. For example, polarization of the sensing electrodes can be pulsed alternately on and off at intervals of 15 milliseconds. It may also be advantageous to alternate polarization, i.e., switch the charge of each electrode at regular intervals.

Sensor **122** is connected to electrometer **126**, which senses small changes in current and translates amps to volts. Voltage signals from electrometer **126** are telemetry conditioned **128** and conveyed to transmitter **130** for radio transmission. All of the components within box **132** are implanted as a single unit in the patient.

Externally, radio signals from transmitter **130**, indicative of glucose concentrations in the patient's blood, are transmitted to receiver **134**. Receiver **134** may be connected to monitor **136** for data monitoring. The same receiver computer or another computer **138** may be used to analyze the raw data and generate glucose concentration information. A printer **140** connected to computer **138** generates hard copies of analyzed data.

The concept of including multiple electrode pairs within a single sensor can be extended to an embodiment where separate sensors are implanted and commonly linked to a single electrometer as shown in FIG. **8**. For example, eight implantable sensors **150** can be implanted in a patient and linked to a single electrometer **152** and transmitter (not shown). Transmitted signals are received by data acquisition adaptor **154** and acquisition computer **156**. By increasing the number of sensors the overall precision, accuracy and longevity of the system can be greatly enhanced. If one or more anodes (or sensors) fails, the others still provide sufficient data sensing capacity so that the entire unit continues to perform satisfactorily. Various algorithms or averaging protocols can be used to process the multiple data streams.

FIG. 9 shows schematically the components of an implantable unit in a glucose sensing system. Implantable unit **160** includes disc-shaped glucose sensor **162** which is connected to electrometer and telemetry conditioning package **164** via anode wire **166***a* and cathode wire **166***b*. Radio signals derived from the raw current signals are transmitted from transmitter element **168**.

Circuitry

FIG. **10** shows custom circuitry structure employed in a glucose sensing system of the present invention. Shown generally at **210** is a glucose servotransmitter suitable for implementation with the present invention. Servotransmitter **210** is configured for transmission of data which is indicative of a sensed enzymatic reaction to a remote receiving source for subsequent processing, the sensing and conveyance of such data being described in detail below.

As shown, servotransmitter **210** includes a sensor **212** (also referred to as a two-electrode sensor) operatively connected between a voltage reference source **214** and an amplifier circuit **216**. The output of circuit **216** is buffered at **218** and subsequently provided to a voltage-to-frequency circuit **220**, which in a first preferred embodiment includes a CMOS 7555 circuit indicated at **220** a configured with a resistive and capacitative network which includes two resistors (R9 and R8) and a capacitor (C2). Utilization of CMOS for designing circuit **220** has been found ideal due to its low power consumption aspects which results in longer battery life. The output terminal of circuit **220** is connected via line **222** to an AC-coupled transmitter **224** (also referred to herein as a minimitter) for transmission of data to an external receiving source.

Discussing the above servotransmitter in more detail, circuit **210** is configured for detecting electrons which are generated during an enzymatic reaction, and conveying data which is representative of such detected electrons to an external source for subsequent processing. More specifically, sensor **212** includes two electrodes, a cathode **212***a* and an anode **212***b*. Cathode **212***a* is connected to a voltage reference source or circuit **214**, and anode **212***b* is connected to amplifier circuit **216**. Voltage reference circuit **214** is made up of three resistor **R4**, **R5**, and **R6** and a 1.2-volt Zener diode Z1. Resistor **R6** is connected at one end to a negative voltage potential, and at the other end to diode Z1 and resistor **R4**. The other end of resistor **R4** is connected to resistor **R5**, which in turn is connected to diode Z1 as shown. The common node between resistors R4 and R5 is connected to cathode **212***a*.

Anode **212***b* is connected via resistors **R3**, **R2**, to the inverting terminal of amplifier **216***a*, and a capacitor C1 is connected between resistors **R3**, R2 and ground. The non-inverting terminal of amplifier **216***a* is tied to ground. A resistor R1 is connected between the output of amplifier **216***a* and its inverting terminal to provide negative feedback.

The output of amplifier **216***a* is connected to the non-inverting terminal of amplifier **218***a*, the output of which is connected to the inverting terminal in a voltage follower configuration for buffering the output of amplifier **216***a*. A resistor **R7** is connected between the output of amplifier **218***a* and the trigger terminal **2** of the CMOS 7555 circuit.

The CMOS 7555 is configured, with its attendant resistive and capacitative network, as a voltage-to-frequency converter whose output frequency is proportional to its input control voltage. Referring more specifically to the 7555, it may be seen that reset terminal **4** is connected to terminal **8**, both of which are connected to a voltage potential which may be referred to as VCC. A resistor **R8** is connected between reset terminal **4** and discharge terminal **7**. A resistor **R9** is connected between discharge terminal **7** and the threshold terminal **6**. A capacitor C2 is connected between trigger terminal **2** and ground. Output terminal **3** is connected to the AC-coupled transmitter **224** for transmission of data to a remote location for processing.

Discussing the operation of the above-described glucose servotransmitter, it will be understood that voltage reference circuit **214** develops a potential of –0.6 volts which is used by sensor **212** to cause electrons produced in the vicinity of the sensor to flow, in the form of a generated current, with amplifier circuit **216**, which includes operational amplifier **216***a* configured for feedback as described above. The output of amplifier **216***a* is a voltage which is buffered at **218** by operational amplifier **218***a*, the voltage output of which controls frequency for the trigger terminal of the CMOS 7555 through resister R7 and frequency selection circuitry C2, R8, and R9. The output terminal **3** of the CMOS 7555 is connected, via line **222**, to transmitter **224** for transmission to an external source.

It will be appreciated that the above-described 7555 configuration converts the output of buffer **218** into a frequency which is determined by the voltage at threshold terminal **6**. The 7555 serves two functions in the above configuration which are necessary for the transmission of sensed data to a remote location for processing. First, the 7555 provides a 15-msec pulse to key transmitter **224**, thereby turning it on and off in accordance with practices which will be understood by those of skill in the art. Second, the 7555 is operable for voltage-to-frequency conversion, which is a measurement of sensor response. This dual function enables the aforementioned data transmission in a manner which will be understood by those of skill in the art.

Preferred component values (resistive and capacitative values) for the above-described servotransmitter **210** are as follows: (1) for voltage reference circuit **214**: R4=1 meg ohm; R5=4.7 meg ohm; and, R6=470 kohm; (2) for amplifier circuit **216**: R1=500 meg ohm; R2 and R3=499 kohm; and, C1=10 pf; (3) for converter circuit **220**: R9=180 kohm; R8=1 meg ohm; and, C2=1 microfarad; and, (4) R7=4.7 meg ohm.

The above system is referred to as a "two electrode" system because of the fact that two electrodes are utilized (the anode and the cathode) in the sensing of electrons produced during a particular enzymatic reaction. Another system which is suitable for sensing produced electrons and conveying data relative to such sensed electrons is a so-called "three-electrode" system which is shown in FIG. **10A** and described briefly below.

In FIG. **10A**, like or similar elements of the three-electrode glucose servotransmitter **210** are labeled to correspond with the two-electrode elements appearing in FIG. **10**. The Figure shows a sensor **212**, a voltage reference source **214**, a voltage-to-frequency converter circuit **220**, and a transmitter **224**. Voltage reference source **214**, voltage-to-frequency converter circuit **220**, and transmitter **224** will not be described because the operation of those elements is the same as, or similar to the operation of such elements as they appear in FIG. **10**.

Sensor **212** in FIG. **10A** varies somewhat from its FIG. **10** counterpart. Such variations take into account some observations regarding current and voltage control which have been made with respect to the two-electrode system described above, and improve somewhat, the control of such

parameters. The three-electrode sensor, set forth at **212**, includes a counter electrode **212***a* (which may be formed from silver), a common return electrode **212***b* (also referred to as a working electrode and which may be formed from platinum), and a voltage probe **212***c*, which may also be termed the reference electrode (and which also may be formed from platinum). Two operational amplifiers **212***d* and **212***e* are provided and operatively coupled to the electrodes as shown, in a configuration which provides greater current and voltage control which, in turn, assists in maintaining the integrity of the electrodes' sensitivity and the ability of the same to detect a produced current which is indicative of an enzymatic reaction. The control is effectuated in a clamped, controlled manner.

The three electrode sensor **212** is shown in FIG. **10**A. Amplifier **212***d* maintains a voltage which is the same as the reference voltage of −0.6 volts between the reference and working electrodes **212***c* and **212***b* respectively. This is accomplished by varying the current at the counter electrode **212***a*, which is in the feedback loop of amplifier **212***d*. Amplifier **212***e* maintains the working electrode **212***b* at virtual ground, converting the current to an output voltage, which is buffered at **212***f* and provided to CMOS 7555 converter circuit **220** for conversion from a voltage to a frequency (in a manner described above), the converter circuit thereafter triggering transmitter **224** in a predeterminable fashion to transmit sensed data indicative of an enzymatic reaction to a remote location for processing.

In a sensor including multiple electrode pairs or multiple anodes, or in sensors including multiple sensor bodies, servotransmitter **210** is modified to incorporate multiple amplifier circuits and buffers, each of which is similar to amplifier circuit **216** aid buffer **218** of servotransmitter **210** shown in FIG. **10**.

To facilitate wireless transmission of multiple signals generated by multiple electrode pairs, converter circuit **220** and the multiple buffers **218** may be replaced in a second preferred embodiment by a single microcontroller. In this second preferred embodiment, a multichannel transmitter includes a microcontroller that samples the amplified signals from multiple amplifier circuits in repetitive sequence, converts the signals to timing data, and outputs the data as sequential pulses separated by pulse periods representing the magnitude of the input signals. The microcontroller of the multichannel transmitter operates as a multiplexer in a manner that will be understood by skilled persons. The output of the microcontroller is transmitted by a radio frequency transmitter circuit as a pulse-period modulated signal and includes a timing signal that facilitates decoding by a remote receiver. Pulse period modulation minimizes the energy used by the sensor for radio frequency transmission. A suitable 4-channel miniature transmitter is manufactured by Minimitter Corporation, of Sunriver, Oreg.

Decreasing Fibrotic Capsule Interference

One of the primary reasons why a subcutanenously-implanted sensor eventually loses its ability to measure the concentration of an analyte of interest is that a collagenous capsule forms around the sensor. The capsule eventually loses vascularity and becomes thick and fibrous, thereby substantially blocking the sensor from accessing the analyte present in blood.

There are at least two promising approaches for minimizing fibrotic capsule interference with analyte detection, thereby extending longevity of an implanted sensor. First, it is possible to prevent or retard capsule formation by slow controlled release of certain collagen deposition inhibitors. Drugs which inhibit collagen formation can be incorporated in a polymer matrix which allows slow release of the drug locally to achieve the desired effect without causing adverse distant systemic effects in the animal or human. For example, collagen inhibitors which can be used for this purpose include corticosteroids such as dexamethasone, relaxin and gamma interferon. A preferred polymer material for carrying and controlling slow release of the drug is polydimethylsiloxane. Corticosteroids can be impregnated in a polydimethylsiloxane matrix so as to provide relatively long-term, slow release of the corticosteroids in the surrounding tissue. It is important, however, that dexamethasone be released in small doses in order to avoid iatrogenic Cushing's syndrome, which is a serious illness caused from systemic excess of corticosteroids. If corticosteroids are released from a sensor for a prolonged period, for example, more than two weeks, we recommend that a patient's serum be tested in order to confirm that adverse systemic effects are avoided.

Another approach for minimizing fibrotic capsule interference with sensor performance, i.e., increasing sensor longevity, is to promote vascularity in the capsule so that the sensor can continue to have access to blood analytes. Accordingly, vascular growth factors can be incorporated in a matrix around the sensor so that the growth factors are slowly released into the surrounding tissue. The released growth factors enhance capillary growth in the collagenous capsule which forms around the implanted sensor. Retention of capillary perfusion by the capsule enhances sensor function by continuously providing the sensor access to the patient's blood analyte. Examples of capillary growth factors include vascular endothelial growth factor (VEGF) and endothelial cell growth factor (ECGF). Polymer materials which are capable of slowly releasing polypeptide factors such as ECGF and VEGF include poly-1-lactic acid and poly glycolic lactic acid. As with the steroid approach, the growth factor dosage, i.e., quantity and rate of release, must be carefully controlled so that the growth factor's effect is local, not systemic.

A method of employing steroids or growth factors to minimize or avoid fibrotic capsule interference with sensor performance, is to provide for the active agent's slow release from the perimeter of the disc sensor. For example, as shown in FIG. **16**A, glucose sensor **300** has a carrier layer or matrix **302** such as a tape made of or containing polydimethylsiloxane impregnated with dexamethasone. Tape **302** is attached to outer perimeter edge **304** of disc-shaped housing or body **306** of sensor **300**. The width of tape **302** is substantially the same dimension as the width of edge **304**, i.e., thickness of housing **306**, so that the steroid is release on or near both faces of the sensor.

Time-release steroid compositions have been utilized in the past for other purposes. For example, U.S. Pat. No. 5,265,608 to Lee et al., the entire content of which is hereby incorporated by reference, discloses a steroid eluding electrode in which dexamethasone is incorporated in a polymer matrix which permits slow controlled release of the steroid to control inflammation, irritation and swelling in connection with a device such as a pacemaker. However, no one has previously employed a time release corticosteroid matrix for inhibiting collagen formation on an implantable analyte sensor.

Sensing Other Analytes

With minor modifications, the sensor designs described above may be used to detect analytes other than glucose. By

changing the specific type of enzyme which covers the anode, the sensor can be used to measure many compounds. Several examples appear in Table 1 below.

TABLE 1

ANALYTE	ENZYME
glucose	glucose oxidase
glucose	hexose oxidase
lactate	lactate oxidase
l-methionine	l-amino acid oxidase
l-phenylalanine	l-amino acid oxidase
d-aspartate	d-amino acid oxidase
d-glutamate	d-amino acid oxidase
urate	urate oxidase
ethyl alcohol	alcohol oxidase
methyl alcohol	alcohol oxidase
cholesterol	cholesterol oxidase
ascorbic acid	ascorbate oxidase

In addition to measuring analytes in body fluids, sensors of the present invention can be used to measure the concentration of substrates in other fluids, for example, fruit and vegetable juices, wine, yogurt, etc.

Construction of a Glucose Sensor

A preferred sensor is constructed of epoxy resin, or of a non-conductive metal, ceramic or other suitable material, in a disc shape, 1.3-centimeters in diameter and 0.2-centimeters in height. Four 36-gauge platinum wires terminate peripherally on one face of the disc (in holes drilled in the resin) and service hydrogen peroxide-sensing anodes. A solid silver cylinder, 0.7-centimeters outside diameter (the cathode), is secured by epoxy resin in the center of the disc. A layer of silver chloride can be deposited onto the surface of the silver by one of several processes. The sensor is preferably double-sided, which may be, for example, two of the four anode sensors configured "back-to-back", making a sensor composed of four anodes and one cathode on each face of the sensor.

Anode and cathode recording wires terminate in an amplifier and polarizing voltage source. An electrometer converts the current signal to a voltage signal and applies a constant polarizing voltage of 0.60 V to the electrodes. Output from the amplifier is routed both to a digital volt meter (Micronta 22-185A, Tandy Corp., Fort Worth, Tex. 76102) and to a strip chart continuous chart recorder (Gould Instruments Model No. 11-2963-300, Valley View, Ohio 44126). The signal can also be routed directly into a computer by use of a data acquisition board. All of these electrical components can be miniaturized without altering their function and carried by a patient on his or her belt, or in a pocket.

A working 8-anode sensor (which has been demonstrated to respond to peroxide) then is selected for testing. The sensor is sanded, first with 600 and 1500 grit wet-or-dry, then followed by a polishing with 2000 grit wet-or-dry. The sensor is rinsed thoroughly in a stream of deionized water (DW) followed by blow drying in a cold nitrogen stream. The sensor is then immersed in an acetone bath and vigorously twirled for 20 seconds to remove any solvents or oils from the surface. The sensor is withdrawn from the acetone bath and is immediately rinsed in a DW stream. The sensor is again blown dry in a cold nitrogen stream, and continues to dry in room air for another 30 minutes.

If it is desired to include an interferent retarding layer, then a layer of PPX (or other suitable membrane material) approximately 5,000–8,000A thick is deposited directly on top of the anodes before depositing any enzyme.

The sanded, cleaned and dried sensor (with or without interferent retarding layer) is enzyme activated with a Glucose Oxidase (GO)—Bovine Serum Albumin (BSA)—Glutaraldehyde (GA) matrix prepared from mixing two parts GO+BSA (20 mg GO+5 mg BSA with 0.5 gram DW) plus one part GA (2.5% GA diluted with DW). Approximately 2.5 μ of this solution is applied via pipette directly to each anode. The solution is allowed to dry in room air for one hour. The sensor is then immersed in DW for 15 minutes to remove excess GA, rinsed briefly in a DW stream, and blown dry in a nitrogen stream. The sensor continues to dry in room air for one hour, after which spin-coating with PU (Tecoflex, Tecothane, Cook composite, or CAR) or vapor deposition with PPX (thickness=3000–5000A) is carried out.

Further miniaturization of the glucose sensor, as described above, will not adversely affect performance of the unit.

Testing, Connecting and Implanting Sensors

Sensors manufactured as described above, are tested the day after they are made by applying a polarizing voltage of 600 mV. The voltage output should stabilize after a one to two hour immersion in a temperature controlled PBS solution (37° C.) in the laboratory water bath. The sensor is tested in standard glucose solutions prepared by adding glucose to PBS so that the resulting test solutions (G=glucose), are concentrated in mg/dl as follows: G(0), G(100), G(200), G(300), G(400) and G(500); and in millimolar concentrations as follows: G(0), G(5.6), G(11.1), G(16.7), G(22.2) and G(27.8). The first data point is collected while the sensor is still immersed in PBS and represents the baseline output. After noting the output value, the sensor is moved to G(100) for ten minutes. The process of measuring the speed with which the sensor responds to the increase in glucose allows calculation of T90 (defined T90 below). The sensor is moved to the G(200) standard and the ten minute output value is collected from this standard. All of the following outputs are collected in ascending order in the same manner.

An implantable sensor has to satisfy three criteria: (1) it must have a T90 of less than three minutes; (2) it must be dose responsive in the glucose concentration range of 40–400 mg/dl; and (3) it must have adequate sensitivity. The T90 value is measured by using the continuous sensor readout provided by the data acquisition system. The point at which 90% of the maximum output is reached (after changing from the zero glucose level to the 100 mg/dl level) is recorded as the T90.

A sensor that is acceptable for implant must also be dose responsive, preferably substantially linear over the glucose concentration of 40–400 mg/dl. Minor to moderate nonlinealities can be mathematically corrected to allow estimation of glucose level from sensor output data.

If a sensor meets all the previous criteria, it is attached to a transmitter. For example, a suitable transmitter may be obtained from Mini-Mitter which has a custom-built interface circuit between the transmitter and the sensor. The transmitter should have a battery pack which is fully charged.

The sensor can be implanted in the body of animals or humans. The sensor can be implanted subcutaneously, in an artery or vein, intramuscularly, intraperitoneally, in the brain or cerebrospinally. The preferred location is subcutaneous. The sensor can also be used in vitro, for example, in a laboratory to measure glucose concentration or other substrates or analytes in a liquid media.

The transmitter and sensor package are tested in vitro the day of the planned implant procedure. If the results are satisfactory (T90 less than 3 minutes, satisfactorily dose-responsive, adequate sensitivity), then the unit is sterilized, rinsed in sterile saline, and implanted subcutaneously in the recipient (after the appropriate preparation and anesthesia procedures).

Experiments

Experiment 1

We compared the performance of sensors with one anode to the performance of sensors with four anodes. Twelve one-sensor anode sensors were constructed substantially as described above. These sensors were similar to the ones shown in FIG. **1** except they only included one anode instead of four, and they only had electrodes on one side of the disc-shaped sensor. All sensors in this experiment were dip-coated with polyurethane (Cook Composites) instead of parylene. Twenty-four-anode sensors were constructed the same as the one-anode sensors except that they included four anodes on one face of the sensor substantially as shown in FIG. **1**.

These sensors were implanted in rats. Glucose dose response data was collected for each of the sensors at frequent time points after implantation until the given sensor failed to perform satisfactorily. For each sensor, the last check point at which the sensor performed adequately, determined the functional life of that sensor.

FIG. **11** shows the results of this experiment. The average longevity for the one-anode sensors was about 4 days. In contrast, the average longevity for the four-anode sensors was about 28 days. This is a highly significant improvement in the functional life of an implanted glucose sensor, which we attribute to the increased number of anodes.

Experiment 2

The purpose of this experiment was to determine in vitro the performance capability in sensors which had failed in vivo. In this experiment, eight of the four anode sensors used in Experiment 1 were tested before implantation (pre-implant), and then tested again after eventually failing to perform and being removed (post-explant) from the rat.

The results of the experiment are shown in FIG. **12**. In FIG. **12** (and FIGS. **13** and **14**), the "Normal Range" includes glucose concentrations which are typically observed in the normal population. The "Dynamic Range" includes the Normal Range plus abnormally high and low glucose concentrations which should be measurable with a glucose sensor. The results show that in vitro the sensors performed as well post-explant as they did pre-implant. This result demonstrates that failure of the sensors in vivo is not due to inactivation or loss of the glucose oxidase enzyme. We noted that over time in vivo a cellular coat tends to envelop the sensor. Before performing the post-explant testing on the sensors, the coats were removed. This suggests that the cellular coat which develops around the sensor may be involved with eventual sensor failure. Since the cellular coat is relatively non-uniform, it is possible to theorize that one of the reasons why longevity is increased with multiple anodes is that the probability of maintaining one or more anodes under a portion of the coat which is minimal enough so that the sensor still performs, is increased by increasing the number or surface area of sensing anodes.

Experiment 3

In Experiments 1 and 2, the sensors were dip-coated in polyurethane (Cook Composites). We subsequently discovered that uniformity and overall performance of the sensors can be improved by using PPX as the outer coat or semi-permeable membrane. The purpose of this experiment was to demonstrate glucose dose response and repeatability for eight sensors, each of which was coated with PPX at a thickness of approximately 3800A. As shown in FIG. **13**, we observed a dose response approaching linearity in the useful measurement range. Test repeatability was also improved with the PPX coated sensors, as shown by the smaller standard deviation margins in comparison to those shown in FIG. **12**.

Experiment 4

This experiment was similar to Experiment 3 except instead of using PPX as the semi-permeable outer membrane, CAR was used. Eight-percent CAR was spin-coated over the surface of the sensor for 2.5 minutes at 4,000 RPM. The sensor was tested in vitro at various glucose concentrations in 3 successive runs. The data is shown in FIG. **14**. The dose response over the useful measurement range approached linearity with a higher slope in comparison to slopes obtained with PPX and dip-coated sensors. We also noted a relatively small standard deviation on repeat tests with the CAR coated sensors.

Experiment 5

This experiment was performed in vitro with PPX coated eight anode (four on each side) sensors to determine how rapidly the sensors respond to changes in glucose concentration (T90). Six sensors were constructed with PPX outer coats of 3000–5000A. Results of this experiment are shown in FIG. **15**. Each of the sensors responded with a T90, i.e., time to reach 90-percent of ultimate current output for a given change in glucose concentration, in less than one minute. This is a faster response time than we had observed previously with polyurethane dip-coated sensors.

What is claimed is:

1. An implantable device for electrochemically sensing changes in the concentration of an analyte of interest, and transmitting signals indicative of the concentration changes, comprising

a transmitter including a power source

a sensor electrically coupled to the transmitter, the sensor including a disc-shaped body having two opposing sides, each side of the sensor body having a cathode and a plurality of anodes, whereby the combined transmitter and sensor can be implanted in a mammal for wireless transmission to an external receiver of data indicative of analyte concentration.

2. The device of claim **1** wherein the analyte of interest is glucose.

3. The device of claim **2** further comprising

an enzyme layer comprising glucose oxidase covering the anodes, and

a membrane semi-permeable to glucose covering the enzyme layer.

4. The device of claim **1** further comprising an amplifier and an electrometer, the cathodes and anodes from the sensor being connected to the amplifier and the electrometer converting current signals into voltage signals before transmitting corresponding data signals to an external processing device.

5. The device of claim **1** further comprising an analog-to-digital converter connected to the sensor for converting analog signals indicative of current changes into digital signals prior to transmitting corresponding data to an external receiver.

6. An analyte concentration monitoring system comprising

a sensor including a sensor body having two opposing sides, each side of the sensor body having at least one

cathode, plural anodes and a semi-permeable membrane covering the anodes, the sensor being capable of generating analog data signals indicative of analyte concentration in a fluid surrounding the sensor,

a transmitter including a power source, the transmitter being electrically coupled to the sensor and capable of converting the data signals into corresponding radio transmission signals

a receiver for receiving the radio transmission signals at a remote location.

7. The system of claim 6 further comprising a processor connected to the receiver for interpreting and converting the radio transmission signals into analyte concentration information.

8. A method of making an implantable analyte sensor comprising

providing a sensor body having two opposing sides,

creating at least one cathode and plural anodes on both sides of the sensor body, and

depositing a semi-permeable membrane on the cathodes and anodes.

9. The method of claim 8 wherein the analyte is glucose, further comprising depositing an enzyme layer including glucose oxidase on the anodes before the step of depositing the semi-permeable membrane.

10. The method of claim 8 wherein the depositing of a semi-permeable membrane includes depositing a layer of polyparaxylxylene or a carbonate-based polyurethane.

11. The method of claim 8 wherein the sensor body is substantially disc-shaped.

12. The method of claim 9 further comprising electrically coupling the sensor to a radio transmitter.

13. The method of claim 12 further comprising

implanting the sensor and transmitter into a mammal,

sensing glucose concentration changes,

transmitting corresponding radio signals to a remote receiver, and

processing and interpreting the radio signals into glucose concentration data.

* * * * *

US006317615B1

(12) **United States Patent**
KenKnight et al.

(10) **Patent No.: US 6,317,615 B1**
(45) **Date of Patent: *Nov. 13, 2001**

(54) **METHOD AND SYSTEM FOR REDUCING ARTERIAL RESTENOSIS IN THE PRESENCE OF AN INTRAVASCULAR STENT**

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(73) Assignee: **Cardiac Pacemakers, Inc.**, St. Paul, MN (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/294,724**

(22) Filed: **Apr. 19, 1999**

(51) **Int. Cl.**[7] **A61B 5/04**

(52) **U.S. Cl.** **600/372**; 600/381; 606/41; 606/194; 606/198

(58) **Field of Search** 606/192, 194, 606/196, 198, 41–50, 32, 33, 34

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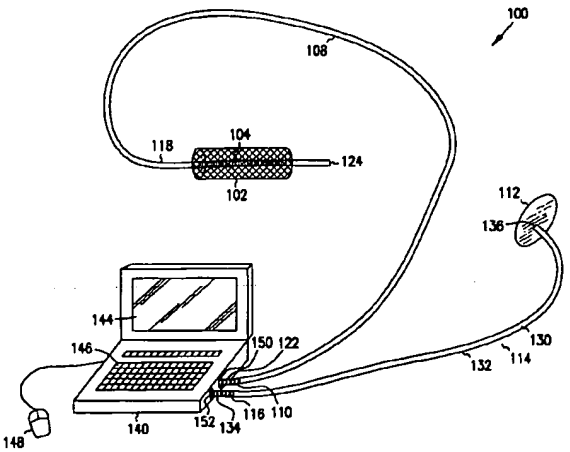
Primary Examiner—Linda C. M. Dvorak
Assistant Examiner—David M. Ruddy
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg, Woessner & Kluth, P.A.

(57) **ABSTRACT**

A first electrode is positioned within an artery proximate an implanted intravascular stent. A second electrode is positioned at a separate location relative the position of the first electrode. Electrical energy is then delivered between the first and the second electrodes to produce an electrical field adjacent the implanted intravascular stent. When a intravascular stent is implanted in a coronary artery, the delivery of the electrical energy is coordinated to cardiac cycles detected in sensed cardiac signals, where the delivery of the electrical energy between the first electrode and the second electrode occurs during a predetermined portion of the cardiac cycle.

18 Claims, 7 Drawing Sheets



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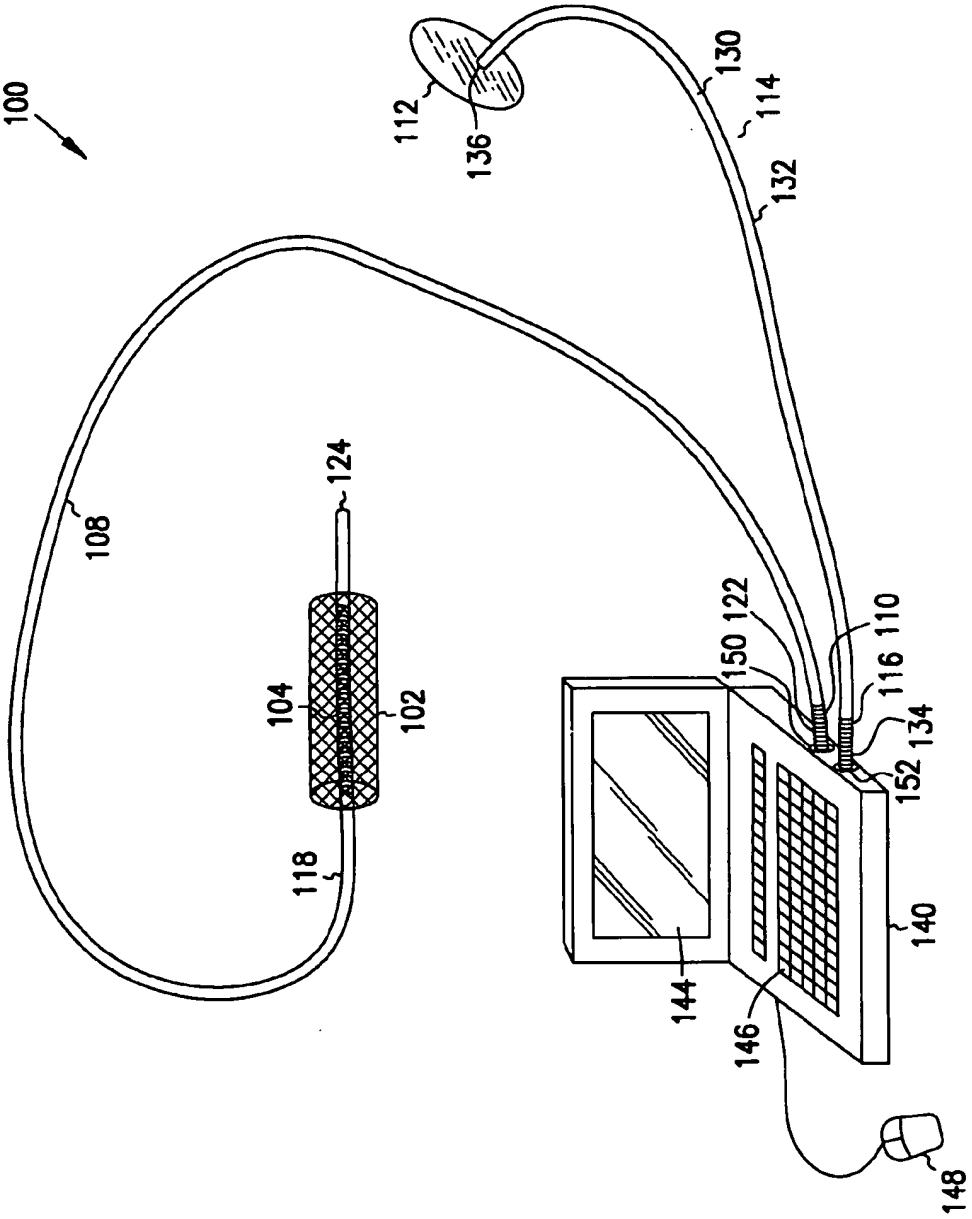
100
112
136
130
114
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118
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134
152
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144
146
148

FIG. 1

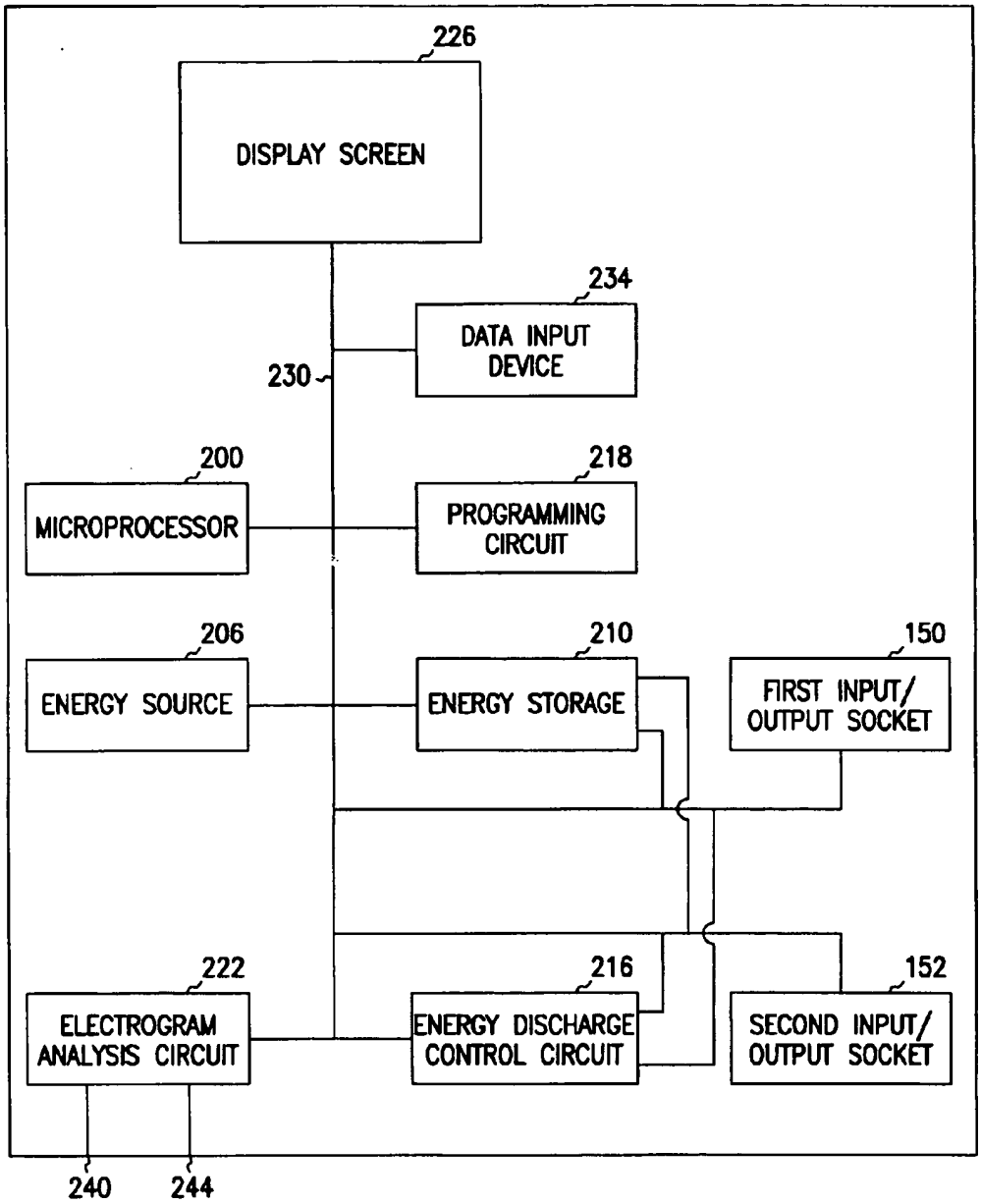

226
DISPLAY SCREEN
234
DATA INPUT DEVICE
230
200
MICROPROCESSOR
218
PROGRAMMING CIRCUIT
206
ENERGY SOURCE
210
ENERGY STORAGE
150
FIRST INPUT/ OUTPUT SOCKET
222
ELECTROGRAM ANALYSIS CIRCUIT
216
ENERGY DISCHARGE CONTROL CIRCUIT
152
SECOND INPUT/ OUTPUT SOCKET
240
244

FIG. 2

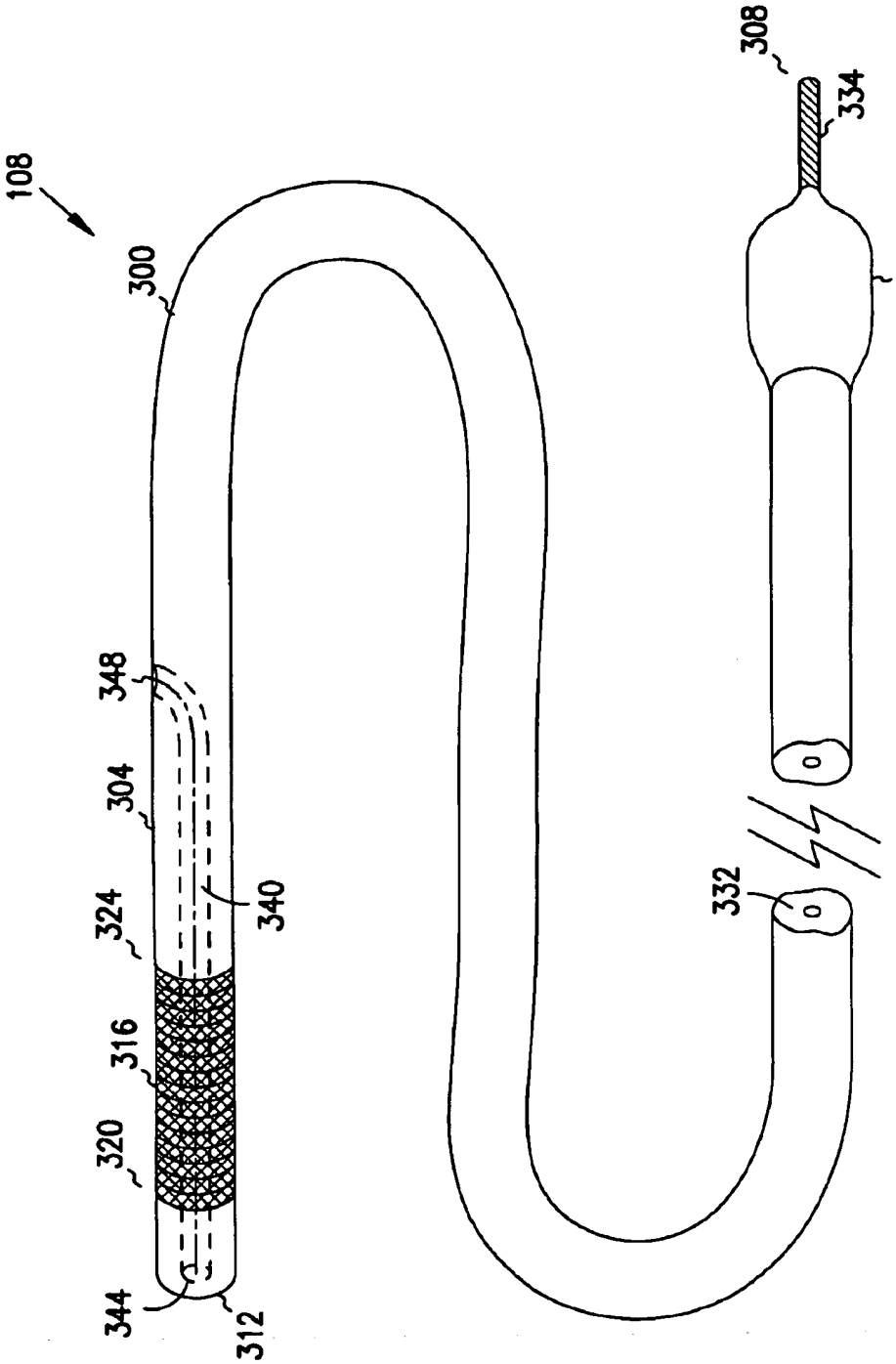


FIG. 3

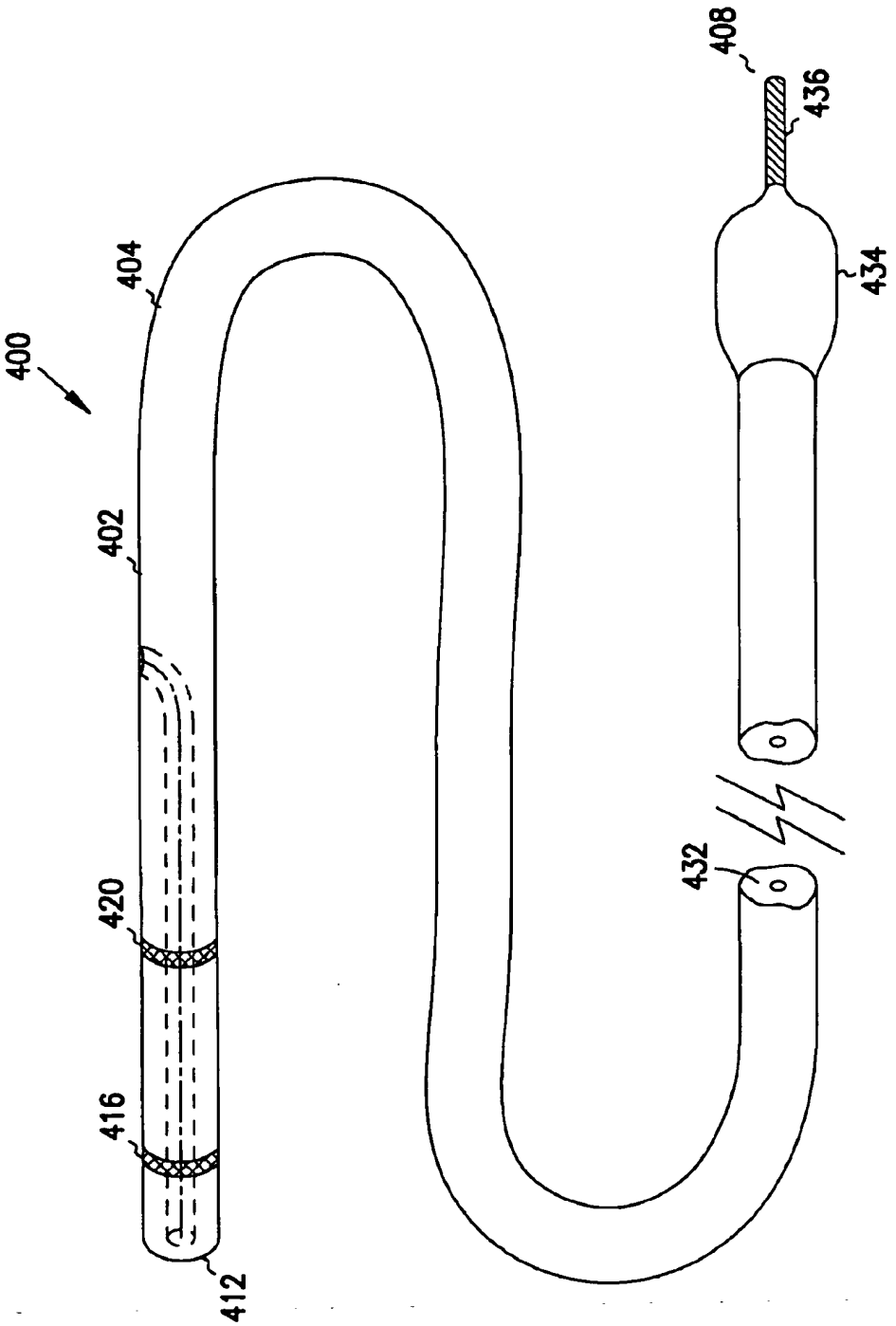


FIG. 4

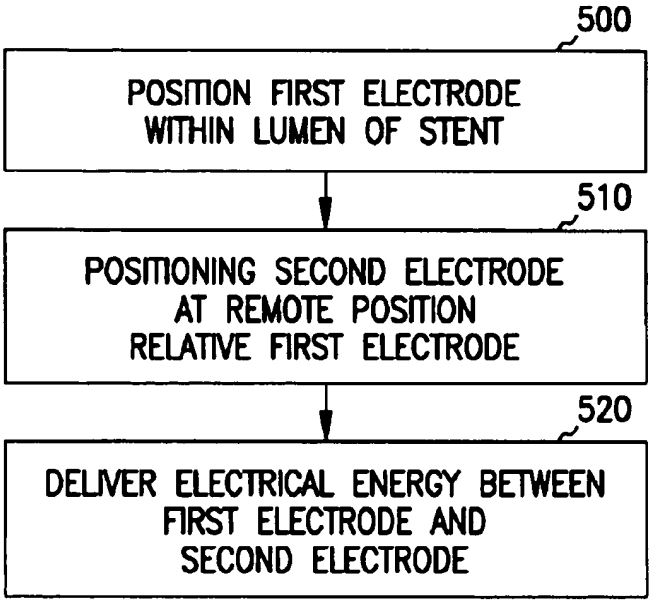

500
POSITION FIRST ELECTRODE WITHIN LUMEN OF STENT
510
POSITIONING SECOND ELECTRODE AT REMOTE POSITION RELATIVE FIRST ELECTRODE
520
DELIVER ELECTRICAL ENERGY BETWEEN FIRST ELECTRODE AND SECOND ELECTRODE

FIG. 5

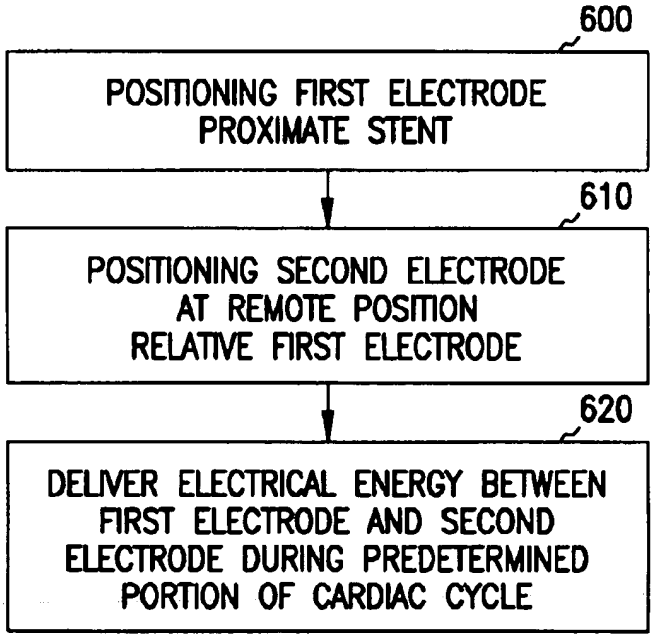

600
POSITIONING FIRST ELECTRODE PROXIMATE STENT
610
POSITIONING SECOND ELECTRODE AT REMOTE POSITION RELATIVE FIRST ELECTRODE
620
DELIVER ELECTRICAL ENERGY BETWEEN FIRST ELECTRODE AND SECOND ELECTRODE DURING PREDETERMINED PORTION OF CARDIAC CYCLE

FIG. 6

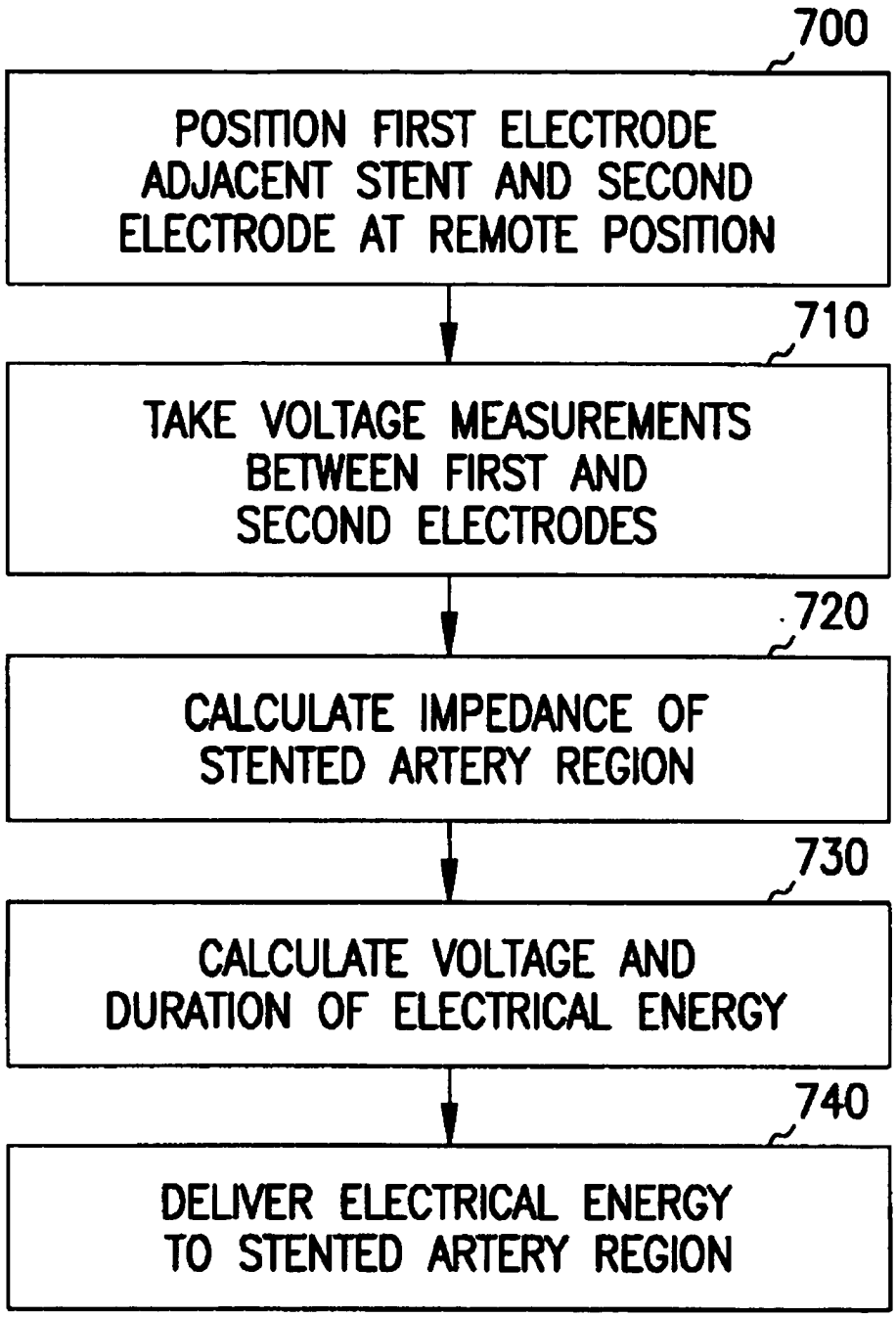
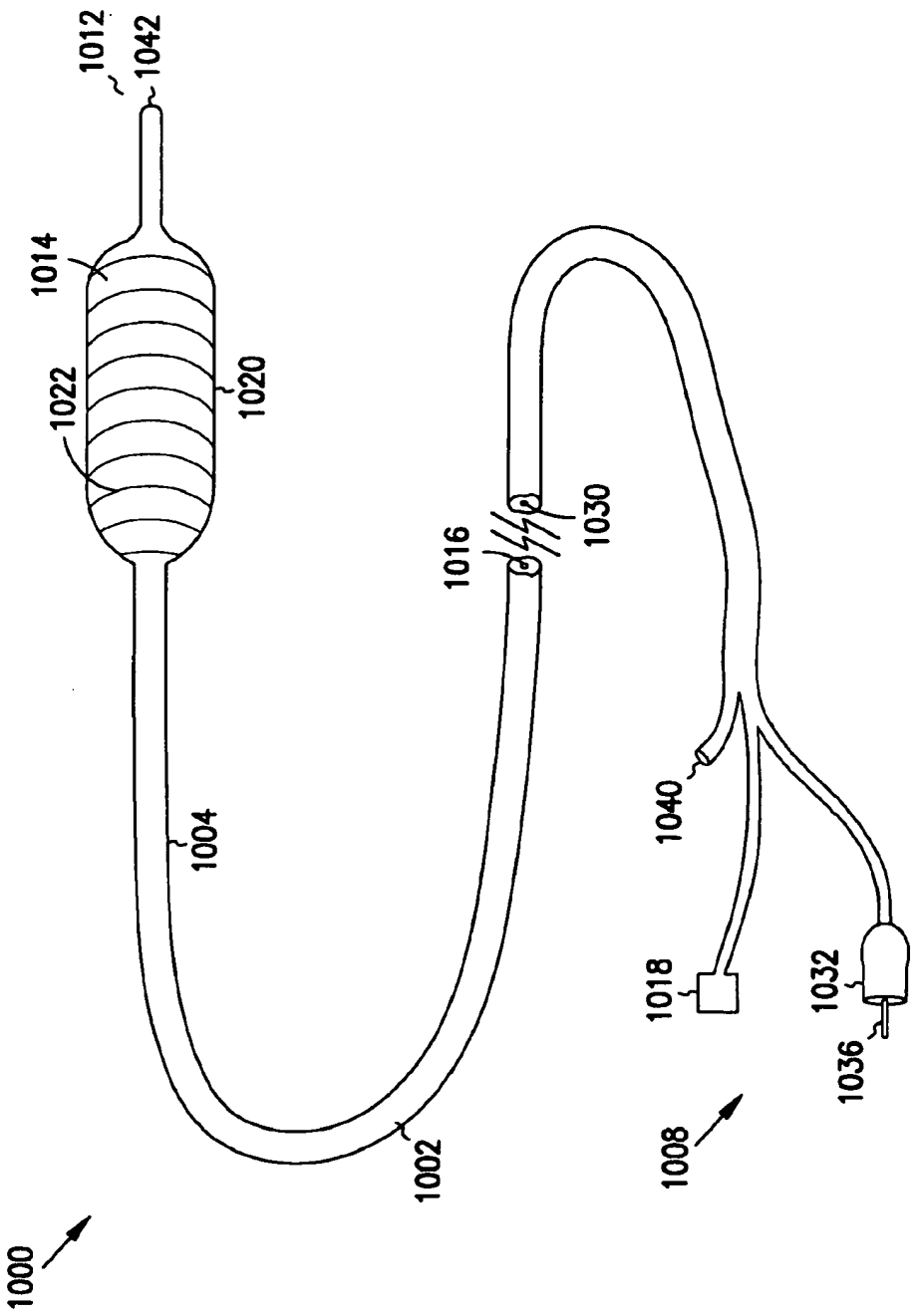

700
POSITION FIRST ELECTRODE ADJACENT STENT AND SECOND ELECTRODE AT REMOTE POSITION
710
TAKE VOLTAGE MEASUREMENTS BETWEEN FIRST AND SECOND ELECTRODES
720
CALCULATE IMPEDANCE OF STENTED ARTERY REGION
730
CALCULATE VOLTAGE AND DURATION OF ELECTRICAL ENERGY
740
DELIVER ELECTRICAL ENERGY TO STENTED ARTERY REGION

FIG. 7


1012
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1016
1030
1004
1040
1018
1032
1036
1002
1008
1000

FIG. 8

METHOD AND SYSTEM FOR REDUCING ARTERIAL RESTENOSIS IN THE PRESENCE OF AN INTRAVASCULAR STENT

FIELD OF THE INVENTION

The present subject matter relates generally to medical devices and more particularly to a method and system for producing an electric field adjacent an intravascular stent.

BACKGROUND OF THE ART

The normal human heart is a strong, muscular pump a little larger than a fist. It pumps blood continuously through the circulatory system. Each day the average heart "beats" (or expands and contracts) 100,000 times and pumps about 2,000 gallons of blood. In a 70-year lifetime, an average human heart beats more than 2.5 billion times.

The heart pumps blood through a circulatory system, which is a network of elastic tubes through which blood flows as it carries oxygen and nutrients to all parts of the body. The circulatory system includes the heart, lungs, arteries, arterioles (small arteries), and capillaries (minute blood vessels). It also includes venules (small veins) and veins, the blood vessels through which blood flows as it returns to the heart.

The circulating blood brings oxygen and nutrients to all the organs and tissues of the body, including the heart itself. The blood also picks up waste products from the body's cells. These waste products are removed as they're filtered through the kidneys, liver and lungs.

Over time, the coronary arteries which supply the heart muscle with blood can become clogged. One cause of clogged arteries is due to a condition called atherosclerosis, or hardening of the arteries. Atherosclerosis causes a constriction of the inner lumen of the affected artery when the lumen of the arteries become more narrow due to a pathological accumulation of cells, fats and cholesterol called plaque. The descriptive term given to this narrowing of the coronary arteries is "stenosis." Stenosis means constriction or narrowing. A coronary artery that is constricted or narrowed is referred to as stenosed. When stenosis of the coronary artery is sufficient to deprive the heart muscle of the oxygen levels necessary for cell viability, the result is typically myocardial infarction, typically referred to as a heart attack.

A heart attack occurs when the blood supply to part of the heart muscle itself, the myocardium, ceases or is severely reduced. This occurs when one or more of the arteries supplying blood to the heart muscle (coronary arteries) becomes partially or completely obstructed by plaque stenoses. If cessation of the blood supply occurs for a long time, heart muscle cells suffer irreversible injury and die. Severe disability or death can result, depending on how much heart muscle is damaged.

Coronary artery bypass surgery is a heart operation used to treat coronary artery disease. In coronary artery bypass surgery a blood vessel is used to go around or "bypass" clogged coronary (heart) arteries. During the "bypass" procedure, a blood vessel from the patient's chest or leg is used as the "bypass" conduit. For venous "bypass" grafts, one end of the vessel is attached to the aorta (the large artery coming out of the heart) and the other end is attached to the coronary artery below the point where it's clogged. Once the clog has been bypassed, blood can once again flow through the bypass graft to the heart, in a manner that prevents ischemia and infarction. Almost half a million coronary bypass operations are performed each year in the USA.

Another procedure for opening clogged coronary arteries is to perform percutaneous transluminal coronary angioplasty, or balloon angioplasty. Balloon angioplasty is an established and effective therapy for some patients with coronary artery disease. Balloon angioplasty is used to dilate (widen) arteries narrowed by plaque. During the procedure, a catheter with a deflated balloon on its tip is passed into the narrowed part of the artery. The balloon in then inflated, and the narrowed area is widened. Balloon angioplasty is a less traumatic and less expensive alternative to bypass surgery for some patients with coronary artery disease. However, in 25 to 30 percent of patients the dilated segment of the artery renarrows (restenosis) within six months after the procedure. The patient may then require either to repeat the balloon angioplasty or to undergo coronary bypass surgery.

One approach to preventing restenosis has been to insert a "stent" across the stenosed area of coronary artery. A stent is a metallic wire mesh tube that is used to prop open an artery that has been recently dilated using balloon angioplasty. The stent is collapsed to a small diameter, placed over an angioplasty balloon catheter and moved into the area of the blockage. When the balloon is inflated, the stent expands, locking in place to form a rigid support (structural scaffolding) which holds the artery lumen open. The stent remains in the artery permanently to help improve blood flow to the heart muscle. However, reclosure (restenosis) remains an important issue with the stent procedure.

Several approaches have been taken to reduce the occurrence of restenosis associated with the stent procedure. Stents have been impregnated with drugs and chemicals that emit radiation (gamma-rays) in an attempt to reduce the frequency of restenosis. Also, drug eluting stents have been used in an attempt to reduce the occurrence of restenosis. However, a need still exists for additional safe and effective treatments to prevent restenosis after the placement of an intravascular stent.

SUMMARY OF THE INVENTION

The present subject matter provides a method and a system for producing electrical energy adjacent an intravascular stent. The electrical energy (or current density) supplied to the artery surrounding the stent is sufficient to structurally modify, damage and/or kill cells within the artery. By effecting the cells of the artery surrounding the stent, it is believed that the occurrence of restenosis associated with the stent procedure will be reduced.

The present subject matter includes a system and method for positioning a first electrode within the vasculature proximate an implanted stent, where the stent is electrically conductive. A second electrode is then positioned at a remote position relative to the first electrode. In one embodiment, the remote position is on the dermal surface of the patient. Cardiac signals are then sensed from the patient. The cardiac signals include cardiac cycles which indicate the electrical events of cardiac excitation. Electrical energy is then delivered between the first electrode and the second electrode during a predetermined portion of a sensed cardiac cycle.

In one embodiment, the first electrode is positioned on a transvenous catheter. The transvenous catheter includes a first lead conductor which is contained within the elongate body of the transvenous catheter and serves to couple the first electrode to the first lead connector. In an additional embodiment, the second electrode is coupled to an external lead. The external lead includes an elongate body and a second lead conductor contained within the elongate body that couples the second electrode to a second lead connector.

The transvenous catheter allows at least a portion of the first electrode to be positioned within the lumen of the implanted stent. Alternatively, the first electrode is positioned entirely within the lumen of the implanted stent. In one embodiment, first electrode is positioned within the lumen of the stent in such a manner that the first and second electrode ends of the first electrode align with the first and second stent ends of the implanted stent, respectively. In one embodiment, the length of the first electrode is between 80 and 120% of the predetermined length of the intravascular stent.

In one embodiment, the first and second electrodes are coupled to a pulse generator. In one embodiment, the pulse generator includes a programming circuit coupled to a display screen, where the programming circuit is used to control the display screen to request parameter values for the electrical energy pulse. The pulse generator further includes a data input device which is coupled to the programming circuit and the display screen. The programming circuit can then receive parameter values for the electrical pulses through the data input device. In one embodiment, the data input device is an alphanumeric keyboard.

In one embodiment, the first and second electrodes are releasably coupled to the pulse generator through a first input/output socket and a second input/output socket, respectively. In one embodiment, cardiac signals are sensed between the first and second electrodes and the cardiac signals are provided to an electrogram analysis circuit. In one embodiment, the electrogram analysis circuit detects cardiac complexes in the sensed cardiac signal. A microprocessor is additionally coupled to the programming circuit, the electrogram analysis circuit and an energy source. The microprocessor receives the parameter values from the programming, circuit and the cardiac complexes in the sensed cardiac signal from the electrogram analysis circuit. The microprocessor also controls the energy source to generate the electrical energy pulse having the parameter values for the intravascular stent when a predetermined portion of a cardiac complex occurs in the cardiac signal.

In an additional embodiment, two or more surface electrocardiogram electrodes are coupled to the pulse generator. The electrogram analysis circuit is adapted to receive one or more cardiac signals (including cardiac complexes) sensed between the two or more surface electrocardiogram electrodes. The microprocessor then controls the energy source to generate the electrical energy pulse having the parameter values for the intravascular stent when a predetermined portion of a cardiac complex occurs in the cardiac signal sensed between the two or more surface electrocardiogram electrodes.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic of a system according to one embodiment of the present subject matter;

FIG. 2 is a block diagram of a pulse generator according to one embodiment of the present subject matter;

FIG. 3 is a schematic of a catheter according to one embodiment of the present subject matter;

FIG. 4 is a schematic of a catheter according to one embodiment of the present subject matter;

FIG. 5 is a flow chart illustrating one embodiment of the present subject matter;

FIG. 6 is a flow chart illustrating one embodiment of the present subject matter;

FIG. 7 is a flow chart illustrating one embodiment of the present subject matter; and

FIG. 8 is a schematic of a catheter according to one embodiment of the present subject matter.

DETAILED DESCRIPTION

In the following detailed description reference is made to the accompanying drawings which form a part hereof and in which is shown by way of illustration specific embodiments in which the invention can be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice and use the invention, and it is to be understood that other embodiments may be utilized and that electrical, logical, and structural changes may be made without departing from the spirit and scope of the present invention. The following detailed description is, therefore, not to be taken in a limiting sense and the scope of the present invention is defined by the appended claims and their equivalents.

Restenosis of arteries after balloon angioplasty continues to be a serious problem. Restenosis has even been found to be a problem after the placement of an intravascular stent which is designed to hold an artery open after balloon angioplasty. The present subject matter addresses the problem of restenosis associated with the stent procedure by providing electrical energy to the artery tissues surrounding the stent. The electrical energy (or current density) supplied to the artery surrounding a stent is sufficient to structurally modify, damage and/or kill cells within the artery.

The general structure of an artery has three layers. The first layer consists of a single continuous layer of endothelial cells along the lumen of the artery. The endothelial cells attach to a second layer, which is a muscular middle layer. This second layer is referred to as the tunica media. The muscular middle layer consists principally of muscular tissue (smooth muscle cells) which are arranged in lamellae and disposed circularly around the vessel. The thickness of the artery wall is due in large part to this muscular middle layer. The third layer is the outer most layer and is referred to as the tunica adventitica. The third layer consists mainly of fine and closely felted bundles of connective tissue and elastic fibers.

An electrical field is localized to the arterial tissue surrounding the stent. In one embodiment, the electrical field is produced in tissues adjacent to the stented region of an artery by effecting a voltage difference between a first electrode positioned adjacent the stent and a second electrode positioned at a remote position relative to the first electrode. The electrical energy is supplied from a capacitor which creates a potential difference (voltage) between the first electrode and the second electrode. The potential difference results in creation of an electric field having a space-varying and time-varying intensity that can be expressed as current density. In one embodiment, the strength of the electrical energy is sufficient to irreparably damage the cells within the structure of the artery, where the cells most heavily damaged are the smooth muscle cells located in the medial layer of the artery. However, the electrical energy is not sufficiently strong to cause significant modification of adjacent myocardial tissue, thereby leaving the remaining cardiac tissue unaffected by the electrical energy.

Referring now to FIG. **1**, there is shown a system **100** according to one embodiment of the present subject matter. The system **100** an intravascular stent **102**, where the intravascular stent **102** in one embodiment is made of metal. The system **100** further includes a first electrode **104**, where the first electrode **104** is positioned on a catheter **108** and is coupled to a first lead connector **110** through a first lead

conductor (not shown). Additionally, the system **100** includes a second electrode **112**, the second electrode **112** positioned on an external lead **114** and is coupled to a second lead connector **116** through a second lead conductor (not shown).

The catheter **108** includes an elongate body **118** having a peripheral surface **120**, a proximal end **122**, and a distal end **124**. The first electrode **104** is positioned on the peripheral surface **120** of the catheter **108** between the proximal end **122** and the distal end **124**. A first lead conductor (not shown) is contained within the elongate body **118** and couples the first electrode **104** to the first lead connector **110** and the proximal end **122**. The catheter **108** further includes a guidewire lumen (not shown) which extends through at least a portion of the elongate body **118**. In an alternative embodiment, the elongate body **118** is adapted to allow the guidewire to extend through the entire length of the elongate body **118**.

The external lead **114** includes an elongate body **130** having a peripheral surface **132**, a proximal end **134**, and a distal end **136**. The second electrode **112** is positioned, or attached, at the distal end **136** of the external lead **114**. A second lead conductor (not shown) is contained within the elongate body **130** and couples the second electrode **112** to the second lead connector **116** at the proximal end **134** of the elongate body **130**. In one embodiment, the second electrode **112** is a patch electrode which is constructed of a conductive gel overlying a metallic foil, as are known.

The system **100** further includes a pulse generator **140**. The pulse generator **140** includes a programming circuit (not shown) and a display screen **144**. The programming circuit is coupled to and controls the display screen **144** to request values for an electrical pulse to be entered into the pulse generator **140**. A data input device is coupled to the programming circuit and display screen **144**. The data input device receives the parameter values for the electrical pulse and displays the values on the display screen **144**. In one embodiment, the data input device is a keyboard **146**. Alternatively, the data input device is a touch sensitive layer (not shown) integrated into the display screen **144** which allow for data input by touching predetermined regions of the layer. Additionally, a computer mouse **148** can be used to supply parameter values, along with other information, by responding to and inputting information presented on the display screen **144**.

The pulse generator **140** further includes a first input/output socket **150** and a second input/output socket **152**. The first and second input/output sockets **150** and **152** are coupled to an electrogram analysis circuit (not shown) housed within the pulse generator **140**. The first lead connector **110** and the second lead connector **116** releasably couple to the first and second input/output sockets **150** and **152**, which allows for electrical signals to be sensed between the first and second electrodes, **104** and **112**. In one embodiment, the electrogram analysis circuit includes signal amplifiers to amplify the electrical signals sensed between the first and second electrodes **104** and **112**.

In one embodiment, the electrical signals sensed between the first and second electrodes **104** and **112** are cardiac signals. The electrogram analysis circuit receives the sensed cardiac signals and analyzes the cardiac signal to detect the occurrence of cardiac complexes in the sensed cardiac signal. In one embodiment, the electrogram analysis circuit detects the occurrence of the QRS-complex of the cardiac complex. Alternatively, the electrogram analysis circuit detects other known portions of the cardiac complex, such as the occurrence of T-waves or the occurrence of the complete cardiac complex.

The pulse generator **140** further includes a microprocessor coupled to the programming circuit, the electrogram analysis circuit and an electrical energy source (not shown). The microprocessor receives the parameter values for the electrical pulse from the programming circuit. Cardiac complexes in the sensed cardiac signal are also provided to the microprocessor from the electrogram analysis circuit. The microprocessor then uses this information to control an energy source to produce the electrical energy pulse having the parameter values when a predetermined portion of a cardiac complex occurs in the cardiac signal. In one embodiment, the microprocessor controls the energy source to generate the electrical energy pulse for the intravascular stent when the predetermined portion of a cardiac complex occurs in the cardiac signal.

In one embodiment, the energy source supplies electrical energy and is coupled to a transducer which converts electrical energy to radio frequency energy. Radio frequency energy is then produced and can be subsequently delivered to the intravascular stent when the predetermined portion of a cardiac complex occurs in the cardiac signal. In an alternative embodiment, the energy source supplies electrical energy to one or more electrical capacitors operatively coupled to the energy source, microprocessor and the first and second input/output sockets **150** and **152**. Upon charging the electrical capacitors to a sufficient energy level, the microcontroller controls the discharge of the electrical capacitors to produce an electrical energy pulse for the intravascular stent.

In one embodiment, the present subject matter is used to deliver electrical energy to an intravascular stent implanted in an artery. Procedures and locations for implanting intravascular stent are known in the art. Once a stent has been implanted in an artery, the cardiac cells adjacent the intravascular stent are altered by providing electrical energy in the region surrounding the stent. In one embodiment, the electrical energy is provided to the region surrounding the stent by discharging electrical energy between the first electrode and the second electrode, where the first electrode is positioned within the artery proximate the implanted stent and the second electrode is positioned at a location that is set apart, or remote, from the first electrode to permit electrical energy to be delivered between the first and second electrodes during a predetermined portion of the cardiac cycle.

In one embodiment, cardiac complexes are sensed by the pulse generator **140** using the first electrode **104** and the second electrode **112**. The sensed cardiac complexes are then used to coordinate the production of the electrical energy for the stent **102**. In one embodiment, the electrogram signals are used by the pulse generator **140** to deliver the electrical energy during the predetermined portion of the sensed cardiac complexes. For example, electrical energy is coordinated to occur during a sensed QRS-complex of the cardiac cycle. Alternatively, the electrical energy is delivered outside the occurrence of the T-wave of the cardiac cycle in a manner that avoids creation of cardiac arrhythmias.

Referring now to FIG. **2**, there is shown a block diagram of one embodiment of the pulse generator **140**. In one embodiment, the pulse generator **140** is a programmable microprocessor based pulse generator. The pulse generator **140** includes a microprocessor **200**, an energy source **206**, energy storage **210**, an energy discharge control circuit **216**, a programming circuit **218**, an electrogram analysis circuit

222, and a display screen 226, wherein the components are electrically connected by bus 230.

The display screen 226 is coupled to the programming circuit 218 by bus 230. In one embodiment, the programming circuit 218 prompts a user through the display screen 226 to input parameters values for the electrical energy pulses to be produced by the pulse generator 140. Parameter values programmable in the pulse generator 140 include, but are not limited to, energy level, voltage, current, number of pulses or shocks to be produced, and duration of each pulse.

Information related to the operation of the electric pulse generator 140 is displayed on the display screen 226. In one embodiment, parameter values and operational commands for the pulse generator 140 are entered through a data input device 234. In one embodiment, the data input device is a keyboard as shown in FIG. 1. The data input device 234 is interactively coupled to the programming circuit 218. Alternatively, the parameter values are provided through the interactive display screen 226, where the display screen 226 has touch sensitive screen to allow parameter values to be entered by touching the display screen 226.

In addition to having parameter values entered into the programming circuit 218, the pulse generator 140 can be used to calculate impedance values for cardiac tissue region surrounding an implanted stent. In one embodiment, the impedance measurements are used to calculate appropriate voltage values for electrical energy pulses generated by the pulse generator 140. In one embodiment, the impedance is determined by producing and delivering a constant current of insufficient magnitude to effect heart contraction from the energy source 206 under the control of the energy discharge control circuit 216 to the first electrode and the second electrode. Alternatively, an alternating current is supplied by the energy source 206 under the control of the energy discharge control circuit 216 to the first electrode and the second electrode.

As the constant current is being delivered across the first and second electrodes, the voltage resulting from the delivered current in sensed by the electrodes. From the measured resultant voltage the microprocessor 200 calculates the impedance of the tissue through which the electrical current passed. The impedance value is then used to calculate a voltage for the electrical energy to be produced by the pulse generator 140. In one embodiment, the electrical energy can then be delivered to the stented region of the artery.

In one embodiment, the first lead connector 110 of the catheter 108 and the second lead connector 116 of the external lead 114 are physically and electrically coupled to the pulse generator 140 through the first input/output socket 150 and the second input/output socket 152. In one embodiment, the polarity of electrical energy delivered to the first input/output socket 150 and a second input/output socket 152 is controlled by energy discharge control circuit 216. In an alternative embodiment, the polarity of the first and second input/output sockets 150 and 152 are fixed as either the cathode terminal or the anode terminal.

The pulse generator 140 further includes the electrogram analysis circuit 222. In one embodiment, the electrogram analysis circuit 222 analyzes one or more sensed electrocardiogram signals. In one embodiment, an electrocardiogram signal is sensed between the first electrode 104 and the second electrode 112. In an alternative embodiment, an electrocardiogram signal is sensed between two or more surface electrodes, where the cardiac signals are provided to the pulse generator 140 through electrocardiogram input sockets 240 and 244 positioned on the pulse generator 140 and electrically coupled to the electrogram analysis circuit 222.

As the electrocardiogram signal is sensed, the electrogram analysis circuit 222 detects the occurrence of QRS-complexes in the signal. The energy discharge control circuit 216 operates to cause the energy source 206 and/or the energy storage 210 to produce electrical energy during the occurrence of QRS-complexes. Alternatively, the electrogram analysis circuit 222 detects the occurrence of both QRS-complexes and T-waves in the sensed cardiac signal. The energy discharge control circuit 216 is then used to ensure the electrical energy is not produced, and then subsequently delivered, during the occurrence of a T-wave.

In one embodiment, when the pulse generator 140 produces the electrical energy, the microprocessor 200 commands the energy source 206 to begin charging energy storage 210. In one embodiment, the energy storage 210 is one or more capacitors as are known in the art. When the energy source 210 has charged to a sufficient energy level, the energy discharge control circuit 216 is used to produce one or more pulses of electrical energy. In one embodiment, the one or more pulses of electrical energy can then be delivered to the first and second input/output sockets 150 and 152 according to the parameter values programmed into the pulse generator 140.

In an alternative embodiment, the pulse generator 140 further includes a transducer (not shown), where the energy source 206 supplies electrical energy and is coupled to the transducer which converts electrical energy to radio frequency energy. The radio frequency energy pulses are then produced by the pulse generator 140 for the intravascular stent.

Referring now to FIG. 3, there is shown one embodiment of the catheter 108 according to the present subject matter. The catheter 108 includes an elongate body 300 having a peripheral surface 304, proximal and distal ends 308 and 312. A first electrode 316 is attached on the peripheral surface 304 of the elongate body 300. In one embodiment, the first electrode 316 is a coil spring electrode which encircles the peripheral surface 304 of the elongate body 300, where the coil spring electrode has a first end 320 and a second end 324. The coil spring electrode provides the region adjacent the distal end 312 with flexibility while still providing a large electrical discharge surface area.

In one embodiment, the length of the first electrode 316 is selected to be between 80 and 120% of the length of an intravascular stent. In an alternative embodiment. the first electrode 316 has a length the range of 6 to 40 millimeters. In an additional embodiment, the length of the first electrode 316 is selected so that first electrode is positioned proximate the intravascular stent with the first electrode within the lumen of the intravascular stent where the first and second electrode ends are aligned with the first and second ends of the stent, respectively. Alternatively, the first electrodes 316 has a length that allows for the first electrode 316 to be positioned completely within the lumen of the stent, or to be positioned with both the first and second ends of the first electrode extending beyond the first and second ends of the stent.

In one embodiment, the first end 320 of the first electrode 316 is spaced longitudinally along the peripheral surface 304 from the distal end 312 by a distance in the range of 2 to 20 millimeters, where 10 millimeters is an acceptable distance. It is understood, however, that the first end 320 of the first electrode 316 can be located at any number of distances from the distal end 312, provided the first electrode 316 can still be positioned adjacent the intravascular stent. An electrical lead 332 extends longitudinally within the elongate

body **300** from a lead connector **330** at the proximal end **308** to electrically connect to the first electrode **316**.

The catheter **108** also includes a lead pin **334** electrically coupled to the electrical lead **332**, where the lead pin **334** is provided at the lead connector **330**. In one embodiment, the lead connector **330** is releasably attach to the pulse generator **140** through the first or second input/output socket **150** or **152**, where lead pin **334** engages a connector terminal within the input/output socket **150** or **152** to electrically couple the first electrode to the pulse generator **140**.

In one embodiment, the elongate body **300** of the catheter **108** is made of an extruded polyurethane biocompatible polymer. In an alternative embodiment, the elongate body **300** of the catheter **108** is made of an extruded silicon rubber. Alternatively, the elongate body **300** of the catheter **108** can be made of any implantable flexible biocompatible polymer (e.g., nylon or polyester) The length of the elongated body **300** of the catheter **108** between the proximal and distal ends **308** and **312** is in the range of 90 to 150 centimeters. Additionally, the diameter of the elongate body **300** is in the range of 1 to 3 millimeters (3 to 9 French). In one embodiment, the diameter of the elongate body **300** is less than the lumenal diameter of the deployed stent.

The electrically conductive lead **332** is constructed of either stainless steel, platinum, or alloys such as MP35N. The first electrode **316** is made of an implantable metal known in the art, such as platinum, titanium, titanium oxide, titanium nitride, carbon, tantalum pentoxide, iridium, or iridium oxide. Other materials suitable for conductor leads and electrodes are also known in the art and are considered to be within the scope of the present subject matter.

The catheter **108** has a guidewire passageway **340** extending longitudinally in the elongate body **300** from an inlet end **344** located at the distal end **312** to a outlet end **348** located along the peripheral surface **304** of the elongate body **300**. In an alternative embodiment, the guidewire passageway **340** extends longitudinally in the elongate body **300** from the inlet end **344** to an outlet end located at the proximal end **308** of the elongate body **300**. In one embodiment, the guidewire passageway **340** is adapted to receive a guidewire for guiding the catheter **108** over the guidewire positioned in the artery. In one embodiment, the guidewire lumen in approximately 20 thousandths of an inch in diameter.

The catheter **108** is relatively flexible at the tip in order to track over the guidewire thus allowing the catheter **108** to advance through patient's arteries. In addition, the catheter includes appropriate axial stiffness (or column strength) at the proximal end **308** to allow for appropriate pushability of the catheter. Choices of catheter design, materials and construction techniques are known which can improve the trackability and the pushability of a catheter intended to be inserted into the arteries. Furthermore, the coil structure of the first electrode **140** allows for improved flexibility and trackability of the catheter over the guidewire.

Referring now to FIG. **4**, there is shown an alternative embodiment of a catheter **400** according to the present subject matter. The catheter **400** includes an elongate body **402** having a peripheral surface **404**, proximal and distal ends **408** and **412**. A first electrode **416** and a third electrode **420** are attached on the peripheral surface **404** of the elongate body **402**. In one embodiment, the first electrode **416** and the third electrode **420** are annular and encircle the peripheral surface **404** of the elongate body **402**.

In one embodiment, the first electrode **416** and the third electrode **420** are spaced apart and spaced longitudinally along the peripheral surface **404** by a distance of between 80 to 120% the length of the intravascular stent. In an alternative embodiment, the first and third electrodes **416** and **420** are spread apart in the range of 6 to 40 millimeters. In addition, the first electrode **416** is spaced longitudinally along the peripheral surface **404** from the distal end **412** by a distance in the range of 2 to 20 millimeters. In one embodiment, the first and third electrodes **416** and **420** are spread apart so the first electrode **416** is positioned adjacent a first end of the stent and the third electrode **420** is positioned adjacent a second end of the stent. It is understood, however, that the first electrode **416** can be located at any number of distances from the distal end **412**, provided the first electrode **416** and the third electrode **420** can be positioned adjacent the intravascular stent.

An electrical lead **432** extends longitudinally within the elongate body **404** from a lead connector **434** at the proximal end **408** to electrically connect the first electrode **416** and the third electrode **420** in common. In one embodiment, a lead pin **436** electrically coupled to the electrical lead **432** is provided at the lead connector **434** to allow the first electrode **416** and the third electrode **420** to be releasably attached and electrically coupled to the pulse generator **140** as previously discussed.

In one embodiment, the elongate body **402** of the catheter **400** is made of an extruded polyurethane biocompatible polymer. In an alternative embodiment, the elongate body **402** of the catheter **400** is made of an extruded silicon rubber biocompatible polymer. Alternatively, the elongate body **402** of the catheter **400** can be made of any implantable flexible biocompatible polymer. The length of the elongated body **402** of the catheter **400** between the proximal and distal ends **408** and **412** is in the range of 90 to 150 centimeters. Finally, the diameter of the catheter is in the range of 1 to 3 millimeters (3 to 9 French), where the diameter of the elongate body is small enough to allow the catheter **400** to pass through the lumen of the intravascular stent.

The electrically conductive lead **432** is constructed of either stainless steel, platinum, or MP35N. The first and third electrodes **416** and **420** are made of an implantable metal known in the art, such as platinum, titanium, titanium oxide, titanium nitride, carbon, tantalum pentoxide, iridium, or iridium oxide. Other materials suitable for conductor leads and electrodes are also known in the art and are considered to be within the scope of the present subject matter.

The catheter **400** has a guidewire passageway **450** extending longitudinally in the elongate body **404** from an inlet end **454** located at the distal end **412** to a outlet end **458** located along the peripheral surface **404** of the elongate body **402**. In an alternative embodiment, the guidewire passageway **450** extends longitudinally in the elongate body **402** from the inlet end **454** to an outlet end located at the proximal end **408** of the elongate body **402**. The guidewire passageway **454** is adapted to receive a guidewire for guiding the catheter **400** over the guidewire positioned in the arteries.

Additionally the catheter **400** is relatively flexible at the tip to track over the guidewire to allow the catheter **400** to advance through patient's arteries. In addition, the catheter **400** includes appropriate axial stiffness (or column strength) at the proximal end **408** to allow for appropriate pushability of the catheter. Catheter design choices, materials and construction techniques are known which can improve the trackability and the pushability of a catheter intended to be inserted into the arteries.

In an alternative embodiment, the third electrode **420** is coupled to a third lead conductor housed within the elongate

body **402**. The third lead conductor is coupled to a lead pin positioned on the lead connector **434**. The input/output socket is adapted to receive the lead connector **434** so that bipolar cardiac signals can be received and bipolar electrical energy can be provided to the first and third electrodes **416** and **420** from the pulse generator **140**. In this present embodiment, electrocardiogram signals used in coordinating the production of electrical energy pulses (e.g., electrical or radio frequency) are sensed from two or more surface electrocardiogram electrodes, where each of the two or more surface electrocardiogram electrodes is coupled to a lead connector of two or more lead connectors which are connected to the pulse generator **140**. In an alternative embodiment, unipolar signals and electrical energy can be produced and supplied across the electrodes by coupling the first and third electrodes in common within the pulse generator **140**.

Referring now to FIG. **5**, there is shown a flow diagram of one embodiment of the present subject matter. At **500**, at least a portion of a first electrode is positioned within a lumen of a stent. In one embodiment, the stent has been implanted within an artery, where the catheter is inserted into the vasculature to align the first and second electrode ends of the first electrode with the first and second stent ends of the stent. At **510**, a second electrode is then positioned at a remote position relative to the first electrode. In one embodiment, the remote position is a portion of skin of the patient in which the first electrode has been positioned. At **520**, electrical energy is then delivered between the first electrode and the second electrode.

Referring now to FIG. **6**, there is shown a flow diagram of an additional embodiment of the present subject matter. At **600**, after placing an intravascular stent in an artery, the catheter is inserted into the vasculature to position either the first electrode (FIG. **3**) or the first and third electrodes (FIG. **4**) in a location proximate the implanted stent. In one embodiment, the electrode is positioned concentrically within the lumen formed by the implanted stent. In one embodiment, the ends of the electrode (e.g., **320** and **324** of FIG. **3**, or **416** and **420** of FIG. **4**) are positioned adjacent to and aligned with the ends of the implanted stent. In an alternative embodiment, the electrode is positioned in a vein or artery that is adjacent to the stented artery. The second electrode is then positioned at a remote position relative to the first electrode at **610**. In one embodiment, the remote position is approximately at the left lateral aspect of the thorax. In an alternative embodiment, the remote position is a dermal surface on the torso. The first and second, or the first, second and third, electrodes are then coupled to the pulse generator. Cardiac signals are then sensed, and electrical energy is delivered between the first electrode and the second electrode (or the first, second and third electrodes) during a predetermined portion of the cardiac cycle at **620**.

Referring now to FIG. **7**, there is shown a flow diagram of an additional embodiment of the present subject matter. At **700**, the first electrode is positioned within an artery proximate an implanted stent. A second electrode, as previously described, is positioned at a remote position relative to the first electrode to allow for the electrical energy to be delivered between the first electrode and the second electrode.

At **710**, voltage measurements are made for the electrical energy by taking bipolar impedance measurements across the first and second electrodes. To make these measurements, a constant low current shock is provided through the electrodes. In one embodiment, the constant low current shock is provided as direct current between the two electrodes. In an alternative embodiment, the current applied between the electrodes is a subthreshold alternating current. In one embodiment, the low current or subthreshold alternating current is delivered in the range of 10 to 50 microamperes. When an alternating current is used, the frequency of current pulses is delivered in the range of 5 to 50 KHz, where 20 KHz is an appropriate value.

A bipolar measurement of the resultant voltage is made using the first and second electrodes. Once the resultant voltage has been measured, the impedance of the stented arterial region is calculated at **720**. In one embodiment, the impedance is determined by using Ohm's law (V=IR) where R is impedance. Once the impedance has been determined, the voltage of the electrical energy required to deliver a specific amount of current is calculated at **730**. In one embodiment, the voltage is calculated by assuming a critical current density. The critical current density is the current density required to effect changes in the cells residing the in the arterial structure. In one embodiment, the critical current density is a predetermined value in the range of 1 to 4 amperes/cm^2. The measured impedance and the critical current density are then used to calculate the voltage of the electrical energy to be delivered across the electrodes.

In one embodiment, the current to the electrode needed to achieve the current density is computed by multiplying the current density by the surface area of the electrode. This is only an approximate calculation since the current density along the electrode will be non-uniform. In one embodiment, an empirically determined correction factor might also be included in the equation to assure the critical current density is achieved along the entire electrode or stented region. Once the current is determined, the voltage is calculated by multiplying current times the impedance. Alternatively, the voltage of the electrical energy to be delivered across the electrodes can be determined by delivering a small voltage shock across the electrodes and measuring the resulting current. Based on the resulting current and the current desired to be delivered to the stented region, a multiplication factor can be calculated by dividing the desired current by the resulting current. The voltage value of the small shock can then be multiplied by the multiplication factor to determine the voltage of the electrical energy necessary to deliver the desired current. For example, if electrical energy delivered at 1.0 volt results in 10 milliamps of current, and it is desired to deliver 5 amps of current, it would then be known that a pulse of electrical energy having a voltage value of 500 volts would be required.

Once the voltage of the electrical energy has been determined, the pulse generator is programmed to deliver the electrical pulses as previously described and the electrical energy is delivered to the stented arterial region under the control of the pulse generator as previously described at **740**.

Besides delivering electrical energy pulses to the stented region of the artery, other types of energy can be delivered. For example, an external defibrillator can use an RLC circuit to store and discharge energy, rather than a capacitor storage and discharge energy. In an additional embodiment, a radio frequency generator could also be used to generate energy to be delivered to the stented region of an artery. In one embodiment, the radio frequency generator is similar to those known in the catheter ablation art.

In addition to the embodiment of delivering electrical energy to stented coronary arteries, the present subject matter can also be used to deliver electrical energy to stents positioned in peripheral arteries. The problem of restenosis is known to be associated with peripheral stents and the

present subject matter can be used in treating the portions of the peripheral vasculature in which a stent has been placed. Portions of the peripheral vasculature in which stents have been placed include the legs and the necks of patients. Therefore, the present subject matter is not limited to treatment of coronary arteries, but rather can include all regions of the vasculature in which a stent might be placed in order to support the structure of the vessel.

Referring now to FIG. **8**, there is shown an alternative embodiment of a catheter **1000** according to the present subject matter. The catheter **1000** includes an elongate body **1002** having a peripheral surface **1004**, a proximal end **1008** and a distal end **1012**. The catheter **1000** further includes an angioplasty balloon **1014** (shown in its expanded state) positioned proximal the distal end **1012** of the catheter **1000**. The elongate body **1002** includes a lumen **1016** extending from an inlet port **1018** positioned at the proximal end **1008** to an outlet end (not shown) which opens into the interior region of the angioplasty balloon **1014**. The inlet and outlet ports are designed to allow fluid to pass under pressure between the inlet and the outlet port for the purpose of expanding and contracting the angioplasty balloon **1014**. Structures and procedures for creating and using catheters having angioplasty balloons are known.

The angioplasty balloon **1014** further includes a peripheral surface **1020**. A first electrode **1022** is positioned on the peripheral surface **1020** of the angioplasty balloon **1014**. In one embodiment, the first electrode **1022** is a flexible conductive layer which is coated onto the peripheral surface **1020** of the balloon **1014**. In an alternative embodiment, the first electrode **1022** is a matrix of flexible conductive wires which are integrated into the peripheral surface **1020** of the balloon **1014**, where portions of the wire surfaces are exposed at the peripheral surface **1020**. The first electrode is coupled to an electrical lead **1030** which extends longitudinally within the elongate body **1002** from a lead connector **1032** at the proximal end **1008** to electrically connect to the first electrode **1022**. In one embodiment, a lead pin **1036** electrically coupled to the electrical lead **1030** is provided at the lead connector **1032** to allow the first electrode **1022** to be releasably attached and electrically coupled to the pulse generator **140** as previously discussed.

In one embodiment, the catheter **1000** has a stent in its unexpanded state positioned over the balloon **1014**. The stent and the balloon are advanced over the guidewire to position the stent in the lumen of an artery to be dilated. The balloon is then inflated. Inflating the balloon **1014** causes the structure of the stent to expand radially to contact and engage the interior surface of the artery. As the balloon is in its inflated position, the first electrode **1022** is in physical contact with the stent. When the stent and the first electrode **1022** are in contact, the pulse generator (as previously described) can be used to generate pulses of electrical energy. In one embodiment, this electrical energy is delivered between the first electrode **1022** and the second electrode, as previously described.

In one embodiment, the first electrode **1022** has a length of between 80 to 120% the length of the intravascular stent. In an alternative embodiment, the first electrode **1022** has a length in the range of 6 to 40 millimeters. In one embodiment, the elongate body **1002** of the catheter **1000** is made of an extruded polyurethane biocompatible polymer. Alternatively, the elongate body **1002** is made from either an extruded nylon or polyester. In addition, the length of the elongated body **1002** between the proximal and distal ends **1008** and **1012** is in the range of 90 to 150 centimeters. Finally, the diameter of the catheter with the angioplasty balloon uninflated is in the range of 1 to 3 millimeters (3 to 9 French).

The electrically conductive lead **1032** is constructed of either stainless steel, platinum, or MP35N. The first electrodes **1022** is made of an implantable metal known in the art, such as platinum, titanium, titanium oxide, titanium nitride, carbon, tantalum pentoxide, iridium, or iridium oxide. Other materials suitable for conductor leads and electrodes are also known in the art and are considered to be within the scope of the present subject matter.

The catheter **1000** further includes a guidewire passageway (not shown) extending longitudinally in the elongate body **1002** from an inlet end **1040** located at the proximal end **1008** to a outlet end **1042** located at the distal end **1012** of the elongate body **1002**. In an alternative embodiment, the guidewire passageway extends longitudinally through a portion of the elongate body **1002** from the inlet end located along the peripheral surface **1004** of the elongate body **1002** to the outlet end located **1042** at the distal end **1012** of the elongate body **1002**. The guidewire passageway is adapted to receive a guidewire for guiding the catheter **1000** over the guidewire positioned in the arteries.

Additionally the catheter **1000** is relatively flexible at the tip to track over the guidewire to allow the catheter **1000** to advance through patient's arteries. In addition, the catheter **1000** includes appropriate axial stiffness (or column strength) at the proximal end **1008** to allow for appropriate pushability of the catheter. Catheter design choices, materials and construction techniques are known which can improve the trackability and the pushability of a catheter intended to be inserted into the arteries.

The present subject matter has now been described with reference to several embodiments thereof. It will be apparent to those skilled in the art that may changes and modifications can be made to the embodiments described without departing from the scope of the present invention. For example, radioopaque markers can be added to the body of the catheter to assist the physician in positioning the electrode adjacent to a stent implanted in a arterial artery.

We claim:

1. A method, comprising:

sensing cardiac signals, where the cardiac signals include a cardiac cycle;

positioning a first electrode within an artery proximate an implanted intravascular stent;

positioning a second electrode at a remote position outside the lumen of the stent; and

delivering at least one pulse of electrical energy between the first electrode and the second electrode during a predetermined portion of the cardiac cycle, at a repetition rate that is on the order of a frequency between heart depolarizations.

2. The method of claim **1**, wherein positioning the second electrode at the remote position includes positioning the second electrode on a dermal surface of a patient.

3. The method of claim **1**, wherein the first electrode is positioned on a catheter, and wherein positioning the first electrode within the artery includes positioning at least a portion of the catheter within the artery to position the first electrode proximate the implanted intravascular stent.

4. The method of claim **3**, wherein at least a portion of the first electrode is positioned within a lumen of the implanted intravascular stent.

5. The method of claim **4**, wherein the first electrode is positioned within the lumen of the implanted intravascular stent.

6. The method of claim **5**, wherein the first electrode has first and second electrode ends and the implanted intravas-

cular stent has first and second stent ends, where positioning the first electrode within the artery includes positioning the first electrode within a lumen of the implanted intravascular stent with the first and second electrode ends aligned with the first and second stent ends, respectively.

7. The method of claim 3, wherein a third electrode is positioned on the catheter proximal the first electrode, and wherein positioning the first electrode includes positioning the catheter within the artery so the first electrode is positioned proximal the implanted intravascular stent and the third electrode is positioned proximal the first electrode along the catheter.

8. The method of claim 7, wherein the implanted intravascular stent has first and second stent ends, and positioning the first electrode and the third electrode includes positioning the first electrode and the third electrode within a lumen of the implanted intravascular stent.

9. The method of claim 1, including physically contacting the first electrode with the implanted intravascular stent.

10. The method of claim 1, wherein the predetermined portion of the cardiac cycle is a QRS-complex of the cardiac cycle.

11. A method, comprising:

positioning at least a portion of a first electrode within a lumen of an intravascularly implanted stent;

positioning a second electrode at a remote position outside the lumen of the stent; and

delivering at least one pulse of electrical energy between the first electrode and the second electrode, at a repetition rate that is on the order of a frequency between heart depolarizations.

12. The method of claim 11, wherein the first electrode has first and second electrode ends and the stent has first and second stent ends, where positioning at least a portion of the first electrode within the lumen of the stent includes positioning the first electrode within the lumen of the stent with the first and second electrode ends aligned with the first and second stent ends, respectively.

13. A method comprising:

sensing cardiac signals, where the cardiac signals include a cardiac cycle;

positioning a first electrode on a catheter within an artery proximate an implanted intravascular stent, including positioning at least a portion of the catheter within the artery to position the first electrode proximate the implanted intravascular stent;

positioning a second electrode at a remote position outside a lumen of the stent;

delivering electrical energy between the first electrode and the second electrode during a predetermined portion of the cardiac cycle; and

wherein a third electrode is positioned on the catheter proximal the first electrode, and wherein positioning the first electrode includes positioning the catheter within the artery so the first electrode is positioned proximal the implanted intravascular stent and the third electrode is positioned proximal the first electrode along the catheter.

14. The method of claim 13, wherein the implanted intravascular stent has first and second stent ends, and positioning the first electrode and the third electrode includes positioning the first electrode and the third electrode within a lumen of the implanted intravascular stent.

15. A method comprising:

sensing a cardiac signal that includes a cardiac cycle;

positioning a first electrode within a vessel near an implanted intravascular stent;

positioning a second electrode at a remote position relative to the first electrode; and

delivering at least one pulse of electrical energy between the first and second electrodes during a predetermined portion of the cardiac cycle, at a repetition rate that is on the order of a frequency between heart depolarizations.

16. The method of claim 15, in which the delivering at least one pulse includes discharging a capacitor.

17. A method comprising:

positioning at least a portion of a first electrode within a lumen of an intravascularly implanted stent;

positioning a second electrode at a remote position relative to the first electrode; and

delivering at least one pulse of electrical energy between the first electrode and the second electrode, at a repetition rate that is on the order of a frequency between heart depolarizations.

18. The method of claim 17, in which the delivering at least one pulse includes discharging a capacitor.

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